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translation of said nucleic acid segment in said cell thereby producing an increased intracellular concentration of said interferon-α polypeptide in said cell which causes the death of said cell.

REMARKS

This communication is responsive to the issues raised by the Examiner in the Office Action dated November 5, 2002 in relation to the above referenced patent application.

A. Time For Response:

Accompanying this response is a petition for a 3 month extension of time pursuant to 1.136(a) and authorization to charge Applicant's deposit account for the requisite fee under 37 C.F.R. 1.17(a)(3) thereby extending the time for response to the pending office action until May 5, 2003. Consequently Applicants believe that this response is timely filed.

B. Request for Continuing Examination:

This communication accompanies a Request for Continuing Examination under (RCE) and payment of the requisite fee. Applicants believe that a RCE is appropriate as prosecution on the merits is closed. Applicants therefore request reconsideration of the pending claims in view of the following and removal of finality of the pending rejections.

C. Status of the Claims:

Applicants note the removal of the rejection of claims 1-4 and 6-9 pursuant to 35 USC 102(e).

Claims 1-4, 7-9, 19-34 and 36-39 stand rejected pursuant to 35 USC 112 as failing to be enabled in view of the teaching of the specification.

Claims 34 and 36-39 stand rejected pursuant to 35 USC 112, second paragraph as failing to particularly point out and claim what the applicant regards as the invention.

Claim 34 is amended by the present communication and is unexamined.

No claim is allowed.

D. Regarding the Amendment to Claim 34:

The amendment to claim 34 is to more distinctly claim the subject matter which applicants regard as their invention. The amendment does not introduce new matter to the specification and grounds for the amendment are provided throughout the specification.

E. Rejection of Claims 34 and 36-39 Pursuant to 35 USC 112, 2nd Paragraph

Claims 34 and 36-39 stand rejected pursuant to 35 USC 112, second paragraph as failing to particularly point out and claim what the applicant regards as the invention. The Examiner indicated that the claims were indefinite because the preamble of the claim provided for a method of achieving a result while the claimed method failed to provide for such effect. Applicants believe that the amended form of Claim 34 (from which claims 36-39 depend) obviates this ground of rejection by specifically providing a method by which the effect provided in the preamble is achieved. Applicants therefore believe that the pending claims 34 and 36-39 are now in compliance with the provisions of 35 USC 112, 2nd Paragraph and respectfully request the removal of this ground of rejection.

F. Rejection Of Claims 1-4, 7-9, 19-34 and 36-39 Pursuant to 35 USC 112, 1st Paragraph:

Claims 1-4, 7-9, 19-34 and 36-39 stand rejected 35 USC 112 in that the teaching of the specification fails to provide a disclosure sufficient to enable one of ordinary skill in the art to practice the full scope of the claimed invention. The Examiner contends that the specification provides only general guidance regarding potential variables involved in the potential use of the compositions of the present invention, particularly in regard to their in vivo therapeutic application, and that the ordinarily skilled artisan would not be able to use the compositions claimed absent more specific information than is provided by the specification. Applicants traverse for reasons of record and as provided below and submit additional evidence to support these positions.

The essence of the pending rejection pursuant to 35 USC 112, 1st paragraph is summed up by the Examiner's assertion that the specification must be something more than a fishing license. However, to extend the metaphor, the law does not require that the Applicant describe in detail

where in the lake the fish are, how deep they are, what type of bait to use and what time of day is best to catch the fish. The disclosure must be written with the ordinarily skilled fisherman in mind. What is needed is to give the ordinary skilled fisherman and idea of what kind of fish he is trying to catch so that he brings the right equipment and pointing the fisherman to general vicinity of the fish. The fisherman can generally take it from there with a reasonable expectation of catching at least one of the fish. This is an appropriate statement of the standard of an enabling disclosure.

In characterizing the teaching of the art, it is necessary that one consider the evolution of the term "gene therapy." The traditional designation of "gene therapy" related to the correction of genetic diseases in human beings by supplying "corrected" versions of defective genes. Because of the ethical issues surrounding fundamental genomic modification of germ line cells, the art has largely moved away from this traditional definition embracing a variety of different technologies that would not fall within the scope of the traditional definition. The term "gene therapy" is presently understood as the delivery of a recombinant DNA molecule to a cell (either in the form of a viral vector, a non-viral delivery system or "naked" DNA) to achieve expression of the encoded genes in the transduced cell. Sometimes, the transduced cell acts as a localized cell factory to produce enhanced localized concentrations of a therapeutic secreted protein. Alternatively, the vector may encode a protein which provides an effect within the cell. Examples include genes which are toxic to the transduced cell which results in its elimination either by direct means (e.g. thymidine kinase plus gancyclovir) or inducing the apoptotic cascade (e.g. p53) or affect other aspects of the transduced cell such as the cell cycle (e.g. p16 and p21). Additionally, recombinant viral vectors which have been specifically engineered to replicate in particular cell types but do not necessarily achieve their objective by production of an exogenous transgene are termed "gene therapy." Some attempts have been made to obviate the confusion in this regard and term such replicating viruses as "virotherapy" rather than gene therapy, but for the moment (and for the purpose of this discussion) such vectors are generally considered gene therapy vectors. The present invention is not directed to "correcting" the sequence of any genes within the cells transduced by the vector.

The analysis of what constitutes an enabling disclosure is based on the Wands factors. Applicants have provided a specific analysis of the present specification in view of these factors in a previous communication. However, review of the most recent office action reveals there are two seminal issues remains unresolved:

(1) the legal issue of the appropriate standard of review, and

(2) the factual issue of the level of skill of ordinarily skilled artisan.

Applicants believe that the following remarks considered in view of the attached information provides sufficient evidence to demonstrate that the present specification is sufficient to support the scope of the pending claims. Consequently, the inquiry is whether or not the skilled artisan would be able to employ the vectors of the present invention in their broadest scope without more teaching than that provided by the specification.

1. Who is the Ordinarily Skilled Artisan in the Field of Gene Therapy?:

Prior to any analysis of what the ordinarily skilled artisan would require is the determination of just who is this oft-cited fictional person of ordinary skill in the art. The applicants have asserted in their prior communications that the level of the ordinarily skilled artisan employing recombinant viral vectors for therapeutic applications, *ex vivo* or *in vivo* is exceptionally high. In the pending office action, the Examiner does not concede nor dispute the qualifications of the ordinarily skilled artisan, but questions rather the predicatability of the art and that undue experimentation would be required. Whether or not undue experimentation would be required to practice the claimed invention is a matter of law independent of the factual inquiry of the qualifications of the ordinarily skilled artisan.[1] *Enzo Biochem, Inc. v. Calgene* (CAFC, 1999). The qualifications of the ordinarily skilled artisan are a question of fact. Ibid. Applicants wish to provide additional information which demonstrates that the level of expertise in this field is exceptionally high.

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[1] The CAFC states, "Whether undue experimentation would have been required to make and use an invention, and thus whether a disclosure is enabling under 35 U.S.C. § 112, ¶ 1, is a question of law that we review de novo, based on underlying factual inquiries that we review for clear error. See Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342, 1354, 47 USPQ2d 1705, 1713 (Fed. Cir. 1998) (citing Wands, 858 F.2d at 736-37, 8 USPQ2d at 1402, 1404)."

Attached to this communication as Exhibit A is a printout of the summary of the pending RAC-approved Human Gene Transfer Protocols obtained from the National Institutes of Health (NIH) website (http://www4.od.nih.gov/oba/rac/clinicaltrial.htm). As can be seen from the extensive number of approved protocols, almost without exception all of these protocols have been performed by those having at least an M.D. degree at a major university teaching hospital or prominent clinical institution (e.g. Fred Hutchinson Cancer Center, Dana-Farber Cancer Center, MD Anderson Cancer Center). The academic and professional backgrounds of these individuals is exceptional. Simply by way of illustration and specifically in relation to the present invention, there are at least five ongoing studies relating to gene therapy with interferon species:

1. A multi-center open label dose escalation study relating to the use of adenoviral delivered interferon beta in the treatment of glioblastoma multiforme at the University of Pennsylvania Medical Center under the direction of Dr. Stephen Eck.
2. A multi-center open label rising dose study of a naked/plasmid DNA encoding interferon alpha in the treatment of unresectable or recurrent/refractory squamous cell carcinoma of the head and neck at the University of Pennsylvania School of Medicine under the direction of Dr. Shelly McQuone
3. An open label multiple administration study of a naked/plasmid DNA encoding interferon alpha in combination with polyvinylpyrrolidone for the treatment of malignant angioendothelioma at the University of Michigan Medical School under the direction of Dr. Lawrence H. Baker
4. An open label multiple administration study of a naked/plasmid DNA encoding interferon alpha and IL-12 in combination with polyvinylpyrrolidone for the treatment of unresectable or recurrent/refractory squamous cell carcinoma of the head and neck at the Tufts University School of Medicine under the direction of Dr. Jeffrey Isner.
5. A Phase I/II multi-center, open label, multiple administration naked/plasmid DNA encoding interferon alpha and IL-12 in combination at the Dana Farber Cancer Institute under the direction of Dr. Marshall Posner.

A brief review of the status of these investigators provides a snapshot of the ordinarily skilled artisan in this field. Marshall Posner, M.D. is the Chief of Head and Neck Oncology at Dana-Farber Cancer Institute. Jeffrey Isner, M.D. (deceased) was Chief of Vascular Medicine and Chief of Vascular Research and was on the Steering Committee of the NIH National Gene Vector Laboratories. Stephen L. Eck, M.D., Ph.D. is a researcher at the Institute for Human Gene Therapy at the University of Pennsylvania Medical Center. Laurence H. Baker, D.O. is the

Director for Clinical Research at the University of Michigan Comprehensive Cancer Center. Shelly McQuone, MD is the chief of the Division of Otolaryngology at the University of Pennsylvania Medical Center. Clearly, these individuals are not only highly qualified physicians but leaders in their field.

Therefore, the Applicants believe that this information demonstrates that the "ordinarily skilled artisan" in the field of clinical gene therapy is a highly trained and specialized physician in an academic medical school at a major university possessing an exceptional academic background.

2. How Much Guidance Does Specification Need to Provide to Enable the Ordinarily Skilled Artisan In the Field of Gene Therapy to Practice the Claimed Invention?

Given the exceptional level of the ordinarily skilled artisan stated above and examiner's position that the pending claims read in their broadest light encompass the *in vivo* administration of a recombinant vector encoding a non-secreted interferon-alpha polypeptide to a human being to achieve intracellular expression of such protein to produce an interferon-alpha effect on the cell in which the polypeptide is produced, how much information does this individual require in order to achieve a reasonable expectation of success? Although there are reported decisions in the field of protein therapeutics and so-called "small molecule" therapeutics, there is a lack of case law that addresses the particular issues relating to the administration of recombinant vectors. Given the lack of case law on point, the applicants attempted to elucidate the standard adopted by the USPTO by analyzing issued patents in view of their disclosures. Since an issued patent is presumed to be enabling for the scope of its claims, in order to elucidate an appropriate standard in this field the applicants engaged in a factual comparison of the scope of issued claims and the corresponding disclosures of the specification. While each application stands on its own, a study of a representative sampling of such disclosures does provide evidence of the appropriate relationship of the disclosure to the claims in this field. As illustrated in that discussion, the level of teaching provided by Applicants' specification is substantially more detailed than that of the patents which have been allowed in this field.

In response to which in the most recent office Action, the Examiner states, "The specification need not be the sole source of the evidence presented." This is true, but the only evidence that an applicant may present to address the question of enablement of the specification is evidence relating to the level of skill in the art and the correct application of the standard. Evidence may not be submitted which supplants the technical teaching of the specification. The specification, independent of the file history, must be enabling. One cannot provide additional evidence to buttress the disclosure without constituting new matter.

Perhaps most probative is the sheer volume of NIH-approved ongoing clinical investigations with recombinant viral vectors demonstrated by in Exhibit 1. The hundreds of approved protocols provide telling evidence of the ability of those of skill in the art to practice gene therapy protocols. Additionally, scientific publications relating to these clinical trials and reference works have been available to the relevant community the provide very detailed guidance regarding methodologies for the application of gene therapy. For example, the book Gene Therapy of Cancer: Methods and Protocols edited by Wolfang Walther and Ulrike Stin (2000, Human Press) provides specific guidance for the clinical application of wide variety of gene therapy agents. A selection of materials from this book are reproduced and attached hereto as Exhibit 2. As one can readily see from the information sampled here, specific guidance relating to patient monitoring dosage, assessment of clinical response, method of administration and preparation of the agents themselves was described in the literature and available to the clinician. Therefore, one of skill in the art given the disclosure available to him would certainly be able to practice the scope of the claimed method.

Addressing other more minor points raised in the Office Action, regarding immunogenicity an repeat dosing. The immunogenicity of adenovirus is well appreciated by those of skill in the art and is recognized as an consideration in the therapeutic use of adenovirus vectors. It is well known that most human beings possess anti-adenoviral antibodies (AAAs) which provide a immunological clearing of some fraction of therapeutic adenoviruses, particularly upon systemic administration. This humoral immune response observed upon the initial dose of such vectors in human individuals which possess pre-existing AAAs and upon

repeat dosing in naïve patient populations. The presence of pre-existing or induced AAAs is not the barrier to therapeutic effect as was speculated. As previously suggested by the Applicants, the references cited by the Examiner are obsolete in view of current clinical experience. There is a large body of data that has demonstrated that it is possible to achieve repeated administration of recombinant human serotype adenoviruses in human beings with therapeutic effect by almost every route of administration as summarized in the table below:

Authors/Citation	Therapeutic Agent	Route of Administration	Dosing Regimen
Hamid, et al (2003) J. Clinical Oncology 21(8):1498-1504	ONYX-015 (a replicating E1b-55K deleted adenovirus vector)	Intravenous	2 x 10e12 viral particles every two weeks for up to two months
Nemunaitis, et al. (2003) Cancer Gene Therapy 10(5):341-352	ONYX-015 (a replicating E1b-55K deleted adenovirus vector)	Intravenous	2 x 10e12 viral particles once per week for six weeks in combination with chemotherapy; second cohort with 2 x 10e11 viral particles daily for five days each week for four consecutive weeks in combination with IL2
Reid, et al (2002) Cancer Research 62(21):6070-79	ONYX-015 (a replicating E1b-55K deleted adenovirus vector)	Intrahepatic arterial infusion	2x10e12 viral particles on days 1 and 8 and in combination with chemotherapy on day 22 every 28 days thereafter
Sze, et al. (2003) J. Vasc Interv Radiol 14(3):279-291	ONYX-015 (a replicating E1b-55K deleted adenovirus vector)	Hepatic arterial infusion	2 x 10e12 particles for two cycles with subsequent cycles combined with chemotherapy
Swisher, et al. (2003) Clinical Cancer Research 9(1): 93-101	INGN 201 (a replication deficient recombinant adenovirus expressing p53)	Intratumoral injection to the lung	Combination study with radiation with INGN 201 being administered on days 1, 18, and 32
Wen, et al (2003) Cancer Gene Therapy 10:224-38	SCH 58500 (a replication deficient recombinant adenovirus expressing p53)	Intraperitoneal Instillation	"multiple cycles" of 7.5x10e13 particles daily for five consecutive days alone and in combination with chemotherapy (gemcitabine)
Buller, et al. (2002) Cancer Gene Therapy 9(7):553-566	SCH 58500 (a replication deficient recombinant adenovirus expressing p53)	Intraperitoneal Instillation	Escalating doses of from 7.5x 10e10 to 7.5 x 10e12; 2-3 doses up to 2.5x10e13 particles per dose for three cycles; 7.5x10e13 particles per day for five days for three weeks, week one alone and weeks 2 and 3 in combination with chemotherapy (carboplatin/paclitaxel)
Kuball, et al. (2002) J. Clin. Oncol. 20(4):957-965	SCH 58500 (a replication deficient recombinant adenovirus expressing p53)	Intratumor injection and intravesical instillation	Three dose levels; 7.5x10e11; 7.5x 10e12; 7.5x10e13 particles per dose; single dose; in combination with Big CHAP formulant

Clearly, these clinical investigators did not believe that the innate or induced immune response precluded repeated dosing in human beings with three different recombinant adenoviruses by any route of administration including systemic intravascular or intravenous administration. These

data clearly dispute the assertions by the Examiner that the pre-existing or induced immunity to viral vectors is a barrier to their effective clinical implementation . Furthermore, the issue of immunogenicity is similar with other viral vectors. Whether the therapeutic virus is a retrovirus, herpesvirus, adeno-associated virus, etc. the immunological response issue would be expected to be similar. Other clinical trials in human beings with other types of vectors have demonstrated that the immunogenicity question, while an issue for consideration, is not a bar.

Finally to address the question of targeting of the therapeutic agents, as previously stated, it is not necessary that the therapeutic agent of the present invention be targeted or be selectively delivered to tumor cells in order to provide an anti-tumor effect. The systemic administration of a recombinant adenoviral vector will result in the infection of a large number of cells, only a few of which will be tumor cells. The same is true of conventional therapeutic agents. In the administration of most anti-cancer agents, of the population of cells attacked by the agent only relatively few are tumor cells. Therefore, the fact that the vector results in the production of the non-secreted interferon (NSI) protein species in cells which are not necessarily cancerous would not suggest that the agent lacks efficacy in the treatment of cancers following systemic administration.

As applicants have repeatedly pointed out, the law does not require that the applicant provide human clinical data to demonstrate efficacy. However, to demonstrate the point, Applicants have presented reports of data from Phase II and Phase III human clinical trial to rebut the Examiner's arguments. These data were obtained provided from large well controlled studies reported in the scientific literature with adenovirus vectors. These reports overwhelmingly rebut the opinions of Verma and Crystal and, at a bare minimum, shifts the burden to the Office to provide scientific data of similar magnitude to rebut the evidence presented.

Conclusion

Applicants therefore believe that they have traversed all grounds of rejection presented in the Office Action and believe that the pending claims are in condition for allowance. Applicants request favorable consideration in light of the foregoing and the art and reasoning of record and request issuance of the present claims without additional delay.

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Dated: May 5, 2003

Respectfully submitted,

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Marked Up Version of the Claims as Amended to Show Changes Made

34. (Amended) A method of killing a hepatocellular carcinoma cell by contacting said hepatocellular carcinoma cell with a recombinant viral vector comprising a nucleic acid segment encoding an interferon-α polypeptide lacking a secretion leader sequence~~, the nucleic acid segment being~~ operatively linked to a liver specific promoter ~~specific for a tissue of interest, wherein the nucleic acid segment encoding the interferon-α polypeptide lacks a secretion leader sequence~~, wherein said vector is internalized by said cell and results in the transcription and translation of said nucleic acid segment in said cell thereby producing an increased intracellular concentration of said interferon-α polypeptide in said cell which causes the death of said cell.

#18

Exhibit 1

Human Gene Transfer Protocols
Last Updated: 02-28-2003

HUMAN GENE TRANSFER PROTOCOLS
Last updated: 02-28-03

8810-001 (Closed) Gene Marking/Cancer
In Vitro/Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *The Treatment of Patients with Advanced Cancer Using Cyclophosphamide, Interleukin-2 and Tumor Infiltrating Lymphocytes.*

*RAC Recommends Approval: 10-3-88/NIH Approval: 3-2-89

9007-002 (Closed) Gene Therapy/Phase I/Monogenic Disease/Severe Combined Immune Deficiency due to Adenosine Deaminase Deficiency
In Vitro/Autologous Peripheral Blood Cells/CD34+ Autologous Peripheral Blood Cells/Cord Blood/Placenta Cells/Retrovirus/Adenosine Deaminase cDNA/Neomycin Phosphotransferase cDNA/Intravenous

Blaese, R. Michael; National Institutes of Health, Bethesda, Maryland; *Treatment of Severe Combined Immune Deficiency (SCID) due to Adenosine Deaminase (ADA) Deficiency with Autologous Lymphocytes Transduced with the Human ADA Gene: An Experimental Study.*

*RAC Recommends Approval: 7-31-90/NIH Approval: 9-6-90

9007-003 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Tumor Infiltrating Lymphocytes/Retrovirus/Cytokine/Tumor Necrosis Factor cDNA/Neomycin Phosphotransferase cDNA/Intravenous

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Gene Therapy of Patients with Advanced Cancer Using Tumor Infiltrating Lymphocytes Transduced with the Gene Coding for Tumor Necrosis Factor.*

*RAC Recommends Approval: 7-31-90/NIH Approval: 9-6-90

9102-004 (Closed) Gene Marking/Cancer/Acute Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Mirro, Joseph; Hurwitz, Craig; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *Autologous Bone Marrow Transplant for Children with Acute Myelogenous Leukemia in First Complete Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse.*

*RAC Recommends Approval: 2-4-91/NIH Approval: 7-12-91
Closed: 1-21-93

9105-005 (Closed) Gene Marking/Cancer/Neuroblastoma
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Mirro, Joseph; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Phase I/II Trial of High Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Stage D Neuroblastoma in First Remission: Use of Marker Genes to Investigate the Biology of Marrow Reconstitution and the Mechanism of Relapse.*

*RAC Recommends Approval: 5-31-91/NIH Approval: 7-12-91
Closed: 9-1-92

9105-006 (Closed) Gene Marking/Cancer/Neuroblastoma
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Mirro, Joseph; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Phase II Trial of High-Dose Carboplatin and Etoposide with Autologous Marrow Support for Treatment of Relapse/Refractory Neuroblastoma Without Apparent Bone Marrow Involvement.*

*RAC Recommends Approval: 5-31-91/NIH Approval: 7-12-91
Closed: 4-9-93

9105-007 (Closed) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; M.D. Anderson Cancer Research Center, Houston, Texas; *Autologous Bone Marrow Transplantation for Chronic Myelogenous Leukemia in which Retroviral Markers are Used to Discriminate between Relapse which Arises from Systemic Disease Remaining after Preparative Therapy Versus Relapse due to Residual Leukemic Cells in Autologous Marrow: A Pilot Trial.*

*RAC Recommends Approval: 5-31-91/NIH Approval: 7-12-91
Closed: 6-1-93
Closed: 4-9-93

9105-008 (Closed) Gene Marking/Acute Hepatic Failure
In Vitro/Autologous Hepatocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intrahepatic

Ledley, Fred D.; Woo, Savio; Ferry, George; and Hartwell, Whisennand; Baylor College of Medicine, Houston, Texas; *Hepatocellular Transplantation in Acute Hepatic Failure and Targeting Genetic Markers to Hepatic Cells.*

*RAC Recommends Approval: 5-30-91/NIH Approval: 7-12-91
Closed: Protocol Never Initiated

9105-009 (Closed) Gene Marking/Cancer/Melanoma
In Vitro/Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Lotze, Michael T.; University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; *The Administration of Interleukin-2 and Tumor Infiltrating Lymphocytes to Patients with Melanoma.*

*RAC Recommends Approval: 5-30-91/NIH Approval: 1-17-92
Closed: 4-95

9110-010 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Renal Cell/Colon/Breast/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Tumor Necrosis Factor cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Tumor Necrosis Factor (TNF).*

*RAC Recommends Approval: 10-7-91/NIH Approval: 10-15-91

9110-011 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Renal Cell/Colon/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Immunization of Cancer Patients Using Autologous Cancer Cells Modified by Insertion of the Gene for Interleukin-2 (IL-2).*

*RAC Recommends Approval: 10-7-91/NIH Approval: 10-15-91

9110-012 (Closed) Gene Therapy/Phase I/Monogenic Disease/Familial Hypercholesterolemia
In Vitro/Low Density Lipoprotein Receptor cDNA/Intrahepatic/Portal Vein Catheter

Wilson, James M.; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Ex Vivo Gene Therapy of Familial Hypercholesterolemia.*

*RAC Recommends Approval: 10-8-91/NIH Approval: 11-14-91
Closed: 3-11-94

9202-013 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Adenocarcinoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DC-Chol/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection/Catheter Delivery to Pulmonary Nodules

Nabel, Gary J.; University of Michigan, Ann Arbor, Michigan; *Immunotherapy of Malignancy by In Vivo Gene Transfer into Tumors.*

*RAC Recommends Approval: 2-10-92/NIH Approval: 4-17-92
Closed: 11-19-92 (Replaced by Protocol #9306-045)

9202-014 (Closed) Gene Marking/Cancer/Acute Myelogenous Leukemia/Acute Lymphocytic Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant
Cornetta, Kenneth; Indiana University, Indianapolis, Indiana; *Retroviral-Mediated Gene Transfer of Bone Marrow Cells during Autologous Bone Marrow Transplantation for Acute Leukemia.*

*RAC Recommends Approval: 2-11-92/NIH Approval: 4-17-92
Closed 5-1-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9202-015 (Closed) Gene Marking/Cancer/Melanoma/Renal Cell
In Vitro/CD4+ Autologous Peripheral Blood Lymphocytes/CD8+ Autologous Peripheral Blood Lymphocytes/CD4+ Autologous Tumor Infiltrating Lymphocytes/CD8+ Autologous Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Economou, James S. and Belldegrun, Arie; University of California at Los Angeles, Los Angeles, California; *The Treatment of Patients with Metastatic Melanoma and Renal Cell Cancer Using In Vitro Expanded and Genetically-Engineered (Neomycin Phosphotransferase) Bulk, CD8 (+) and/or CD4(+) Tumor Infiltrating Lymphocytes and Bulk, CD8(+) and/or CD4(+) Peripheral Blood Leukocytes in Combination with Recombinant Interleukin-2 Alone, or with Recombinant Interleukin-2 and Recombinant Alpha Interferon.*

*RAC Recommends Approval: 2-11-92/NIH Approval: 4-17-92
Closed: 6-94

9202-016 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraperitoneal Administration

Freeman, Scott M.; Tulane University Medical Center, New Orleans, Louisiana; *Gene Transfer for the Treatment of Cancer.*

*RAC Recommends Approval: 2-10-92/NIH Approval: 2-5-93

9202-017 (Open) Gene Therapy/Infectious Disease/Human Immunodeficiency Virus
In Vitro/CD8+ Allogeneic Cytotoxic T Lymphocytes/CD8+ Syngeneic Cytotoxic T Lymphocytes/Retrovirus/Hygromycin Phosphotransferase/Herpes Simplex Virus Thymidine Kinase cDNA/Intravenous

Greenberg, Philip D. and Riddell, Stanley; Fred Hutchinson Cancer Research Center, University of Washington, Seattle; *Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy Using Genetically Modified CD8+ HIV-Specific T Cells in HIV Seropositive Individuals.*

*RAC Recommends Approval: 2-11-92/NIH Approval: 4-17-92

9206-018 (Closed) Gene Therapy/Phase I/Cancer/Relapsed-Refractory Neuroblastoma/Immunotherapy
In Vitro/Autologous Neuroblastoma Cells/Allogeneic Partially HLA-Matched/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Brenner, Malcolm K.; Furman, Wayne; Santana, Victor; Bowman, Laura; and Meyer, William; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Cytokine-Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma.*

*RAC Recommends Approval: 6-1-92/NIH Approval: 8-14-92

9206-019 (Closed) Gene Therapy/Phase I/Cancer/Brain/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Stereotactic Injection

Oldfield, Edward; National Institutes of Health, Bethesda, Maryland; *Gene Therapy for the Treatment of Brain Tumors Using Intra-Tumoral Transduction with the Thymidine Kinase Gene and Intravenous Ganciclovir.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 6-1-92/NIH Approval: 8-14-92
Closed: 12-94

9206-020 (Closed) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; MD Anderson Cancer Center, Houston, Texas; *Use of Two Retroviral Markers to Test Relative Contribution of Marrow and Peripheral Blood Autologous Cells to Recovery After Preparative Therapy.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92
Closed: 2-13-96

9206-021 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Partially HLA-Matched/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Gansbacher, Bernd; Houghton, Alan; and Livingston, Philip; Memorial Sloan Kettering Cancer Center, New York, New York; *Immunization with HLA-A2 matched Allogeneic Melanoma Cells that Secrete Interleukin-2 in Patients with Metastatic Melanoma.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92
Closed: 10-19-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9206-022 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vitro/Allogeneic Partially HLA-Matched/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Gansbacher, Bernd; Motzer, Robert; Houghton, Alan; and Bander, Neil; Memorial Sloan Kettering Cancer Center, New York, New York; *Immunization with Interleukin-2 Secreting Allogeneic HLA-A2 Matched Renal Cell Carcinoma Cells in Patients with Advanced Renal Cell Carcinoma.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92

9206-023 (Closed) Gene Marking/Cancer/Multiple Myeloma
In Vitro/CD34+ Autologous Peripheral Blood Cells/Intravenous/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; *Retroviral-Mediated Gene Transfer of Bone Marrow and Peripheral Blood Stem Cells During Autologous Bone Marrow Transplantation for Multiple Myeloma.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92

9206-024 (Closed) Gene Marking/Cancer/Breast
In Vitro/CD34+ Autologous Peripheral Blood Cells/Intravenous/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; *Retroviral-Mediated Gene Transfer of Bone Marrow and Peripheral Blood Stem Cells During Autologous Bone Marrow Transplantation for Metastatic Breast Cancer.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92

9206-025 (Closed) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/CD34+ Autologous Peripheral Blood Cells/Intravenous/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; *Retroviral-Mediated Gene Transfer of Bone Marrow and Peripheral Blood Stem Cells During Autologous Bone Marrow Transplantation for Chronic Myelogenous Leukemia.*

*RAC Recommends Approval: 6-2-92/NIH Approval: 8-14-92

9209-026 (Closed) Gene Marking/Infectious Disease/Human Immunodeficiency Virus
In Vitro/Syngeneic Peripheral Blood Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Tavel, Jorge; National Institutes of Health, Bethesda, Maryland; *A Study of the Safety and Survival of the Adoptive Transfer of Genetically Marked Syngeneic Lymphocytes in HIV Infected Identical Twins.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 9-3-93
Closed to new enrollment. Individuals will be followed, long-term, in a new protocol (that does not involve administration of recombinant DNA): 1-17-02

9209-027 (Closed) Gene Marking/Cancer
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Schuening, Friedrich G.; Miller, A. Dusty; and Kiem, Hans-Peter; Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; *Study on Contribution of Genetically Marked Peripheral Blood Repopulating Cells to Hematopoietic Reconstitution after Transplantation.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 2-5-93
Closed: 4-29-97

9209-028 (Closed) Gene Marking/Cancer/Lymphoid Malignancies/
In Vitro/G-CSF Mobilized Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Schuening, Friedrich G.; Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; *Evaluation of the Use of Recombinant Human G-CSF Stimulated Peripheral Blood Progenitor Cell Supplementation in Autologous Bone Marrow Transplantation in Patients with Lymphoid Malignancies.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 2-5-93
Closed: 2-25-94 (Merged with protocol # 9209-027)

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9209-029 (Closed) Gene Marking/Cancer/
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Schuening, Friedrich G.; Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington; *A Trial of G-CSF Stimulated Peripheral Blood Stem Cells for Engraftment in Identical Twins.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 2-5-93
Closed: Protocol Never Initiated

9209-030 (Open) Gene Marking/Cancer/Chronic Lymphocytic Leukemia/Follicular Non-hodgkins Lymphoma
In Vitro/Autologous Bone Marrow Cells/Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; University of Texas MD Anderson Cancer Center, Houston, Texas; *Use of Retroviral Markers to Identify Efficacy of Purging and Origin of Relapse Following Autologous Bone Marrow and Peripheral Blood Cell Transplantation in Indolent B Cell Neoplasms (Follicular Non-Hodgkin's Lymphoma or Chronic Lymphocytic Leukemia) Patients.*

*RAC Recommends Approval: 9-14-92/NIH Approval: 12-2-93

9403-031 (Open) Gene Therapy/Phase I/Cancer/Non-small Cell Lung Cancer/Antisense/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Retrovirus/p53 cDNA/kras Antisense/Intratumoral/Bronchoscope

Roth, Jack A.; The University of Texas MD Anderson Cancer Center, Houston, Texas; and Garver, Robert I., Jr.; University of Alabama at Birmingham, Birmingham, AL; *Clinical Protocol for Modification of Oncogene and Tumor Suppressor Gene Expression in Non-Small Cell Lung Cancer (NSCLC).*

*RAC Recommends Approval: 3-4-94/NIH Approval: 1-4-95

9209-032 (Closed) Gene Marking/Cancer/Neuroblastoma
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; St. Jude Children's Research Hospital, Memphis, Tennessee; *A Phase II Trial of the Baxter Neuroblastoma Bone Marrow Purging System Using Gene Marking to Assess Efficacy.*

*RAC Recommends Approval: 9-15-92/NIH Approval: 2-5-93

9209-033 (Open) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vitro/Autologous Fibroblasts/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Retrovirus/Cytokine/Interleukin-4 cDNA/Subcutaneous Injection

Lotze, Michael T. and Rubin, Joshua T.; University of Pittsburgh, Pittsburgh, Pennsylvania; *Gene Therapy of Cancer: A Pilot Study of IL-4 Gene Modified Antitumor Vaccines.*

*RAC Recommends Approval: 9-15-92/NIH Approval: 2-5-93

9212-034 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Crystal, Ronald G.; Rockefeller University Hospital, New York, New York; *A Phase I Study, in Cystic Fibrosis Patients, of the Safety, Toxicity, and Biological Efficacy of a Single Administration of a Replication Deficient, Recombinant Adenovirus Carrying the cDNA of the Normal Human Cystic Fibrosis Transmembrane Conductance Regulator Gene in the Lung.*

*RAC Recommends Approval: 12-3-92/NIH Approval: 4-16-93
Protocol closed, IND inactive: 5-30-00

9212-035 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/E2a Temperature Sensitive Mutant/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Wilson, James M., University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; Simon, Richard H., University of Michigan Medical Center, Ann Arbor, Michigan; McCoy, Karen, Cystic Fibrosis Center at Ohio State University; *Gene Therapy of Cystic Fibrosis Lung Diseases Using E1 Deleted Adenoviruses: A Phase I Trial.*

*RAC Recommends Approval: 12-3-92/NIH Approval: 8-26-93

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9212-036 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal

Welsh, Michael J.; Howard Hughes Medical Institute, Iowa City, Iowa; and Smith, Alan E.; Genzyme Corporation, Framingham, Massachusetts; *Cystic Fibrosis Gene Therapy Using an Adenovirus Vector: In Vivo Safety and Efficacy in Nasal Epithelium.* Sponsor: Genzyme Corporation

*RAC Recommends Approval: 12-4-92/NIH Approval: 4-16-93
Protocol ended in November 1993

9303-037 (Closed) Gene Therapy/Phase I/Cancer/Glioblastoma/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Van Gilder, John C.; University of Iowa, Iowa City, Iowa; Berger, Mitchell; University of California, San Francisco, California; Prados, Michael; University of Washington, Seattle, Washington; Warnick, Ronald; University of Cincinnati Medical Center, Cincinnati, Ohio; Schold, Clifford; University of Texas Southwestern Medical Center, Dallas, Texas; Fetell, Michael; Columbia Presbyterian Medical Center, New York, New York; Schramm, Johannes; Neurochirurgische Universitatsklinik, Bonn, Germany; Westphal, Manfred; University Clinic Eppendorf, Hamburg, Germany; Tonn, Jorg-Christian; University Kliniken, Wurzburg, Germany; Moumdjian, Robert; Notre-Dame Hospital, Montreal, Quebec, Canada; Shaffrey, Mark; University of Virginia, Charlottesville, Virginia; Asher, Anthony; Charlotte Neurological Associates and Presbyterian Hospital, Charlotte, North Carolina; Epstein, Mel; Brown University, Providence, Rhode Island; Schmitz-Schackert, Gabriele Anna Maria; University Klinikum Karl-Gustav-Carus, Dresden, Germany; Mendez, Ivar; Victoria General Hospital, Nova Scotia, Canada; Bernstein, Mark; The Toronto Hospital, Toronto, Ontario, Canada; *Gene Therapy for the Treatment of Recurrent Glioblastoma Multiforme with In Vivo Tumor Transduction with the Herpes Simplex Thymidine Kinase Gene/Ganciclovir System.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 3-1-93/NIH Approval: 4-16-93

9303-038 (Open) Gene Marking/Cancer/Leukemia/Non-malignant Disorders
In Vitro/Epstein-Barr Virus Specific Allogeneic Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Heslop, Helen E.; Brenner, Malcolm K.; and Rooney, Cliona; St. Jude Children's Research Hospital, Memphis, Tennessee; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes to Recipients of Mismatched-Related or Phenotypically Similar Unrelated Donor Marrow Grafts.*

*RAC Recommends Approval: 3-2-93/NIH Approval: 4-16-93

9303-039 (Closed) Gene Marking/Cancer/Acute Myelogenous Leukemia
In Vitro/Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Brenner, Malcolm K.; Krance, Robert; Heslop, Helen E.; Santana, Victor; and Ihle, James; St. Jude Children's Research Hospital, Memphis, Tennessee; *Assessment of the Efficacy of Purging by Using Gene-Marked Autologous Marrow Transplantation for Children with Acute Myelogenous Leukemia in First Complete Remission.*

*RAC Recommends Approval: 3-2-93/NIH Approval: 4-16-93

9303-040 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Subcutaneous Injection

Simons, Jonathan; Johns Hopkins Oncology Center, Baltimore, Maryland; *Phase I Study of Non-Replicating Autologous Tumor Cell Injections Using Cells Prepared With or Without Granulocyte-Macrophage Colony Stimulating Factor Gene Transduction in Patients with Metastatic Renal Cell Carcinoma.*

*RAC Recommends Approval: 3-1-93/NIH Approval: 12-2-93
Study closed, long-term follow-up continues: 7-16-01

9303-041 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Wilmott, Robert W. and Whitsett, Jeffrey; Children's Hospital Medical Center, Cincinnati, Ohio; and Trapnell, Bruce; Genetic Therapy, Inc., Gaithersburg, Maryland; *A Phase I Study of Gene Therapy of Cystic Fibrosis Utilizing a Replication Deficient Recombinant Adenovirus Vector to Deliver the Human Cystic Fibrosis Transmembrane Conductance Regulator cDNA to the Airways.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 3-2-93/NIH Approval: 4-16-93
Closed: 4-28-97 (IND Withdrawn)

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9303-042 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator CDNA/Intranasal

Boucher, Richard C. and Knowles, Michael R.; University of North Carolina, Chapel Hill, North Carolina; *Gene Therapy for Cystic Fibrosis Using E1 Deleted Adenovirus: A Phase I Trial in the Nasal Cavity.*

*RAC Recommends Approval: 3-2-93/NIH Approval: 10-7-93
Closed: 10-94

9306-043 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Gamma Interferon cDNA/Subcutaneous Injection

Seigler, Hilliard F.; Duke University Medical Center, Durham, North Carolina; and Merritt, James A.; Viagene, Inc., San Diego, California; *A Phase I Trial of Human Gamma Interferon-Transduced Autologous Tumor Cells in Patients With Disseminated Malignant Melanoma.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93

9306-044 (Closed) Gene Therapy/Phase I/Cancer/Ovarian/Chemoprotection
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Bone Marrow Transplant

Deisseroth, Albert B.; Kavanagh, John; and Champlin, Richard; University of Texas MD Anderson Cancer Center, Houston, Texas; *Use of Safety-Modified Retroviruses to Introduce Chemotherapy Resistance Sequences into Normal Hematopoietic Cells for Chemoprotection During the Therapy of Ovarian Cancer: A Pilot Trial.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 12-2-93

9306-045 (Closed) Gene Therapy/Phase I/Cancer/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection/Catheter Delivery to Pulmonary Nodules

Nabel, Gary J.; University of Michigan Medical Center, Ann Arbor, Michigan; *Immunotherapy for Cancer by Direct Gene Transfer into Tumors.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93

9306-046 (Closed) Gene Therapy/Phase I/Monogenic Disease/Gaucher Disease
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Glucocerebrosidase cDNA/Bone Marrow Transplant

Barranger, John A.; University of Pittsburgh, Pittsburgh, Pennsylvania; *Gene Therapy for Gaucher Disease: Ex Vivo Gene Transfer and Autologous Transplantation of CD34(+) Cells.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93

9306-047 (Closed) Gene Therapy/Phase I/Monogenic Disease/Gaucher Disease
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Glucocerebrosidase cDNA/Bone Marrow Transplant

Karlsson, Stefan and Dunbar, Cynthia; National Institutes of Health, Bethesda, Maryland; and Kohn, Donald B.; Childrens Hospital Los Angeles, Los Angeles, California; *Retroviral Mediated Transfer of the cDNA for Human Glucocerebrosidase into Hematopoietic Stem Cells of Patients with Gaucher Disease.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93
Closed: 4-30-97 (IND Withdrawn)

9306-048 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Galpin, Jeffrey E.; University of Southern California; Casciato, Dennis A.; Shared Medical Research Foundation, Tarzana, California; and Merritt, James A.; Viagene, Inc., San Diego, California; *A Preliminary Study to Evaluate the Safety and Biologic Effects of Murine Retroviral Vector Encoding HIV-1 Genes [HIV-IT(V)] in Asymptomatic Subjects Infected with HIV-1.* Sponsor: Chiron Corporation

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93
Closed: 9-8-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9306-049 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense In Vitro/CD4+ Autologous Peripheral Blood Cells/Retrovirus/Particle Mediated Gene Transfer (Accell®)/RSV-tar/Rev M10/Intravenous

Nabel, Gary J.; University of Michigan Medical Center, Ann Arbor, Michigan; *A Molecular Genetic Intervention for AIDS - Effects of a Transdominant Negative Form of Rev.*

*RAC Recommends Approval: 6-7-93/NIH Approval: 9-3-93

IND terminated: 3-13-00

9306-050 (Open) Gene Therapy/Phase I/Cancer/Astrocytoma/Pro-Drug In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Ommaya Injection

Raffel, Corey; Mayo Clinic, Rochester, Minnesota; Villablanca, Judith; Childrens Hospital Los Angeles, Los Angeles, California; Packer, Roger, Childrens National Medical Center, Washington, DC; Tonn, Jorg-Christian, Neurochirurgische Klinik und Poliklinik, Universitats-Klinikin, Wurzburg, Germany; and Burdach, Stefan; University Center for Paediatrics, Heinrich-Heine Universitat, Dusseldorf, Germany; *Gene Therapy for the Treatment of Recurrent Pediatric Malignant Astrocytomas with In Vivo Tumor Transduction with the Herpes Simplex Thymidine Kinase Gene.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 6-8-93/NIH Approval: 9-3-93

9306-051 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Brain/Chemoprotection In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Bone Marrow Transplant

Hesdorffer, Charles and Antman, Karen; Columbia University College of Physicians and Surgeons, New York, New York; *Human MDR Gene Transfer in Patients with Advanced Cancer.*

*RAC Recommends Approval: 6-8-93/NIH Approval: 9-3-93

9306-052 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Antisense In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin (Gibco BRL)/Insulin-like Growth Factor Antisense/Subcutaneous Injection

Ilan, Joseph; Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, Ohio; *Gene Therapy for Human Brain Tumors Using Episome-Based Antisense cDNA Transcription of Insulin-Like Growth Factor I.*

*RAC Recommends Approval: 6-8-93/NIH Approval: 12-2-93

9309-053 (Open) Gene Therapy/Phase I/Cancer/Small Cell Lung Cancer/Immunotherapy In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin (Gibco BRL)/Cytokine/Interleukin-2 cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Podack, Eckhard R.; Sridhar, Kasi; University of Miami; and Savaraj, Niramol; Miami Veterans Administration Hospital, Miami, Florida; *Phase I Study of Transfected Cancer Cells Expressing the Interleukin-2 Gene Product in Limited Stage Small Cell Lung Cancer.*

*RAC Recommends Approval: 9-9-93/NIH Approval: 12-2-93

9309-054 (Open) Gene Therapy/Phase I/Cancer/Breast/Chemoprotection In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Intravenous

O'Shaughnessy, Joyce; Kentuckiana Medical Oncology Association, Louisville, Kentucky; *Retroviral Mediated Transfer of the Human Multi-Drug Resistance Gene (MDR-1) into Hematopoietic Stem Cells During Autologous Transplantation after Intensive Chemotherapy for Breast Cancer.*

*RAC Recommends Approval: 9-9-93/NIH Approval: 10-7-93

9309-055 (Open) Gene Therapy/Phase I/Cancer/Brain Tumors/Pro-Drug In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Kun, Larry E.; Sanford, R. A.; Brenner, Malcolm K.; and Heideman, Richard L.; St. Jude Childrens Research Hospital, Memphis, Tennessee; and Oldfield, Edward H.; National Institutes of Health, Bethesda, Maryland; *Gene Therapy for Recurrent Pediatric Brain Tumors.* Sponsor: Genetic Therapy,
Inc./Novartis

*RAC Recommends Approval: 9-9-93/NIH Approval: 10-7-93

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9309-056 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Interleukin-2 cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Das Gupta, Tapas K. and Cohen, Edward P.; University of Illinois at Chicago, Chicago, Illinois; *Immunization of Malignant Melanoma Patients with Interleukin 2-Secreting Melanoma Cells Expressing Defined Allogeneic Histocompatibility Antigens.*

*RAC Recommends Approval: 9-10-93/NIH Approval: 4-19-94

9309-057 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition/Hairpin Ribozyme
In Vitro/CD4+ Peripheral Blood Cells/Retrovirus/Hairpin Ribozyme/Intravenous

Wong-Staal, Flossie; Poeschla, Eric; and Looney, David; University of California, San Diego, California; *A Phase I Clinical Trial to Evaluate the Safety and Effects in HIV-1 Infected Humans of Autologous Lymphocytes Transduced with a Ribozyme that Cleaves HIV-1 RNA.*

*RAC Recommends Approval: 9-10-93/NIH Approval: 10-25-94

9309-058 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Retrovirus/Interleukin-2 cDNA/Subcutaneous Injection

Economou, James S. and Glaspy, John A.; University of California Medical Center, Los Angeles, California; *Genetically Engineered Autologous Tumor Vaccines Producing Interleukin-2 for the Treatment of Metastatic Melanoma.*

*RAC Recommends Approval: 9-10-93/NIH Approval: 12-2-93

9312-059 (Closed) Gene Therapy/Phase I/Cancer/Leptomeningeal Carcinomatosis/Pro-Drug
In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraventricular Injection/Subarachnoid Injection

Oldfield, Edward H. and Ram, Zvi; National Institutes of Health, Bethesda, Maryland; *Intrathecal Gene Therapy for the Treatment of Leptomeningeal Carcinomatosis.* Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 12-2-93/NIH Approval: 1-20-94
Closed: 1/95

9312-060 (Open) Gene Therapy/Phase I/Cancer/Colon/Immunotherapy
In Vitro/Autologous Fibroblasts/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Retrovirus/Interleukin-2 cDNA/Subcutaneous Injection

Sobol, Robert E. and Royston, Ivor; San Diego Regional Cancer Center, San Diego, California; *Injection of Colon Carcinoma Patients with Autologous Irradiated Tumor Cells and Fibroblasts Genetically Modified to Secrete Interleukin-2.*

*RAC Recommends Approval: 12-2-93/NIH Approval: 1-4-95

9312-061 (Closed) Gene Therapy/Phase I/Monogenic Disease/Gaucher Disease
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/Glucocerebrosidase cDNA/Intravenous

Schuening, Friedrich; Fred Hutchinson Cancer Research Center, Seattle, Washington; *Retrovirus-Mediated Transfer of the cDNA for Human Glucocerebrosidase into Peripheral Blood Repopulating Cells of Patients with Gaucher's Disease.*

*RAC Recommends Approval: 12-2-93/NIH Approval: 11-15-94
Closed: 4-29-97

9312-062 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Haubrich, Richard; University of California at San Diego Treatment Center, San Diego, California; and Merritt, James A.; Viagene, Inc., San Diego, California; *An Open Label, Phase I/II Clinical Trial to Evaluate the Safety and Biological Activity of HIV-IT(V) (HIV-1 IIIBenv/rev Retroviral Vector) in HIV-1 Infected Subjects.*

*RAC Recommends Approval: 12-3-93/NIH Approval: 4-19-94
Closed: 10-13-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9312-063 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin (Gibco BRL)/B7 (CD80) cDNA/Neomycin Phosphotransferase cDNA/Subcutaneous Injection

Sznol, Mario; National Institutes of Health, Frederick, Maryland; *A Phase I Trial of B7-Transfected Lethally Irradiated Allogeneic Melanoma Cell Lines to Induce Cell Mediated Immunity Against Tumor-Associated Antigens Presented by HLA-A2 or HLA-A1 in Patients with Stage IV Melanoma.*

*RAC Recommends Approval: 12-3-93/NIH Approval: 4-19-94

9312-064 (Closed) Gene Therapy/Phase I/Cancer/Colon/Hepatic Metastases/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Hepatic Injection

Rubin, Joseph; Mayo Clinic, Rochester, Minnesota; *Phase I Study of Immunotherapy of Advanced Colorectal Carcinoma by Direct Gene Transfer into Hepatic Metastases.* Sponsor: Vical, Incorporated

*RAC Recommends Approval: 12-3-93/NIH Approval: 4-19-94
Closed: 3-16-95 (Closed to accrual - maximum number of subjects entered)

9312-065 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Used in Combination with Anti-CD3 and Interleukin-2 Primed Autologous Lymph Node Cells to Prime Autologous Peripheral Blood Cells In Vitro/Retrovirus/GM-CSF cDNA/Intravenous

Chang, Alfred E.; University of Michigan, Ann Arbor, Michigan; *Adoptive Immunotherapy of Cancer with Activated Lymph Node Cells Primed In Vivo with Autologous Tumor Cells Transduced with the GM-CSF Gene.*

*RAC Recommends Approval: 12-3-93/NIH Approval: 8-23-94

9312-066 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Cationic Liposome Complex/DMRIE-DOPE/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal

Sorscher, Eric J. and Logan, James L.; University of Alabama, Birmingham, Alabama; *Gene Therapy for Cystic Fibrosis Using Cationic Liposome Mediated Gene Transfer: A Phase I Trial of Safety and Efficacy in the Nasal Airway.*

*RAC Recommends Approval: 12-3-93/NIH Approval: 1-4-95

9312-067 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Maxillary Sinus Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Maxillary Sinus Administration

Welsh, Michael J.; Howard Hughes Medical Institute, Iowa City, Iowa; *Adenovirus-Mediated Gene Transfer of CFTR to the Nasal Epithelium and Maxillary Sinus of Patients with Cystic Fibrosis.* Sponsor: Genzyme Corporation

*RAC Recommends Approval: 12-3-93/NIH Approval: 2-10-94
Protocol ended in May 1995

9403-068 (Closed) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Gamma Interferon cDNA/Subcutaneous Injection

Rosenblatt, Joseph; University of California, Los Angeles, California; Seeger, Robert; Childrens Hospital, Los Angeles, California; and Merritt, James A.; Viagene, Inc., San Diego, California; *A Phase I Study of Immunization with Gamma Interferon Transduced Neuroblastoma Cells.*

*RAC Recommends Approval: 3-3-94/NIH Approval: 10-25-94

9403-069 (Closed) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vitro/CD8+ Syngeneic Peripheral Blood Cells/Retrovirus/CD4-zeta Chimeric Receptor/Intravenous/Concurrent Interleukin-2 Therapy

Walker, Robert; National Institutes of Health, Bethesda, Maryland; *A Phase I/II Pilot Study of the Safety of the Adoptive Transfer of Syngeneic Gene-Modified Cytotoxic T-Lymphocytes in HIV-Infected Identical Twins.* Sponsor: NIH/Cell Genesys, Inc.

*RAC Recommends Approval: 3-3-94/NIH Approval: 8-23-94
Closed: 2-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9403-070 (Open) Gene Therapy/Phase I/Monogenic Disease/Alpha-1-Antitrypsin Deficiency
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Cationic Liposome Complex/DC-Chol-DOPE/Alpha-1 Antitrypsin cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Brigham, Kenneth; Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; *Expression of an Exogenously Administered Human Alpha-1-Antitrypsin Gene in the Respiratory Tract of Humans.* Sponsor: Gene Medicine, Inc.

*RAC Recommends Approval: 3-3-94/NIH Approval: 10-25-94

9403-071 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection

Vogelzang, Nicholas; the University of Chicago, Chicago, Illinois; *Phase I Study of Immunotherapy for Metastatic Renal Cell Carcinoma by Direct Gene Transfer into Metastatic Lesions.* Sponsor: Vical, Incorporated

*RAC Recommends Approval: 3-4-94/NIH Approval: 4-19-94
Closed: 4-5-95 (Closed to accrual - maximum number of subjects entered)

9403-072 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral/Direct Injection

Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; and Akporiaye; Harris; Stopeck; Unger; and Warneke; University of Arizona, Tucson, Arizona; *Phase I Study of Immunotherapy of Malignant Melanoma by Direct Gene Transfer.* Sponsor: Vical, Incorporated

*RAC Recommends Approval: 3-4-94/NIH Approval: 4-19-94
Closed: 3-27-95 (Closed to accrual - maximum number of subjects entered)

-9406-073 (Open) Gene Therapy/Phase I/Colon/Immunotherapy
In Vivo/Autologous Tumor Cells/Plasmid DNA/Carcinoembryonic Antigen Plasmid Expression Vector/Kanamycin Resistance cDNA/Intratumoral/Direct Injection

Curiel, David; University of Alabama, Birmingham, Alabama; *Phase I Trial of a Polynucleotide Augmented Anti-Tumor Immunization to Human Carcinoembryonic Antigen in Patients with Metastatic Colorectal Cancer.*

*RAC Recommends Approval: 6-10-95/NIH Approval: 7-27-95

9406-074 (Closed) Gene Therapy/Phase I/Other/Rheumatoid Arthritis
In Vivo/Autologous Synovial Cells/Retrovirus/Interleukin-1 Receptor Antagonist Protein cDNA/Intrajoint/Metacarpal Phalangeal Joints

Evans, C. H. and Robbins, Paul; University of Pittsburgh, Pittsburgh, Pennsylvania; *Clinical Trial to Assess the Safety, Feasibility, and Efficacy of Transferring a Potentially Anti-arthritic Cytokine Gene to Human Joints with Rheumatoid Arthritis.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 7-27-95

9406-075 (Closed) Gene Marking/Cancer/Ovarian
In Vitro/Autologous Peripheral Blood Cells/Autologous Tumor Infiltrating Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intraperitoneal

Freedman, Ralph; MD Anderson Cancer Center, Houston, Texas; *Use of a Retroviral Vector to Study the Trafficking Patterns of Purified Ovarian TIL Populations Used in Intraperitoneal Adoptive Immunotherapy of Ovarian Cancer Patients: A Pilot Study.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 7-12-94

9406-076 (Closed) Gene Marking/Cancer/Pediatric Malignancies
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Heslop, Helen; Brenner, Malcolm, K.; and Krance, Robert; St. Jude Childrens Research Hospital, Memphis, Tennessee; *Use of Double Marking with Retroviral Vectors to Determine the Rate of Reconstitution of Untreated and Cytokine Expanded CD34(+) Selected Marrow Cells in Patients Undergoing Autologous Bone Marrow Transplantation.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 7-12-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9406-077 (Closed) Gene Therapy/Phase I/Cancer/Breast/Chemoprotection
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Intravenous

Deisseroth, Albert; Hortobagyi, Gabriel; Champlin, Richard; and Holmes, Frankie; MD Anderson Cancer Center, Houston, Texas; *Use of Safety-Modified Retroviruses to Introduce Chemotherapy Resistance Sequences into Normal Hematopoietic Cells for Chemoprotection During the Therapy of Breast Cancer: A Pilot Trial.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 7-12-94

9406-078 (Closed) Gene Therapy/Phase I/Monogenic Disease/Fanconi Anemia
In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Fanconi Anemia Complementation Group C cDNA/Intravenous

Liu, Johnson, M. and Young, Neal S.; National Institutes of Health, Bethesda, Maryland; and Wagner, John E., University of Minnesota, Minneapolis, Minnesota; *Retroviral Mediated Gene Transfer of the Fanconi Anemia Complementation Group C Gene to Hematopoietic Progenitors of Group C Patients.*

*RAC Recommends Approval: 6-9-94/NIH Approval: 2-12-95
Closed: 1997, follow-up continuing

9406-079 (Closed) Gene Therapy/Phase I/Cancer/Non-small Cell Lung Cancer/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral/Bronchoscope

Roth, Jack A.; MD Anderson Cancer Center, Houston, Texas; *Clinical Protocol for Modification of Tumor Suppressor Gene Expression and Induction of Apoptosis in Non-Small Cell Lung Cancer (NSCLC) with an Adenovirus Vector Expressing Wildtype p53 and Cisplatin.*

*RAC Recommends Approval: 6-10-94 and 9-11-95/NIH Approval: 9-21-95

9406-080 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Immunotherapy
In Vitro/Autologous Fibroblasts/Lethally Irradiated/In Combination with Untransduced Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Sobol, Robert and Royston, Ivor; San Diego Regional Cancer Center; San Diego, California; *Injection of Glioblastoma Patients with Tumor Cells Genetically Modified to Secrete Interleukin-2 (IL-2): A Phase I Study.*

*RAC Recommends Approval: 6-10-94/NIH Approval: 7-12-94

9406-081 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Lymphoma/Breast/Head and Neck Cancer/Immunotherapy
In Vitro/Autologous Fibroblasts/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-12 cDNA/Neomycin Phosphotransferase cDNA/Intratumoral/Direct Injection

Lotze, Michael T; University of Pittsburgh, Pittsburgh, Pennsylvania; *IL-12 Gene Therapy Using Direct Injection of Tumor with Genetically Engineered Autologous Fibroblasts.*

*RAC Recommends Approval: 6-10-94/NIH Approval: 2-10-95

9408-082 (Closed) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Subcutaneous Injection

Simons, Jonathan; Johns Hopkins Oncology Center, Baltimore, Maryland; *Phase I/II Study of Autologous Human GM-CSF Gene Transduced Prostate Cancer Vaccines in Patients with Metastatic Prostate Carcinoma.*
NIH/ORDA Approval: 8-3-94 (Accelerated Review)

Study closed, long-term follow-up continues: 7-16-01

9409-083 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)

Zeitlin, Pamela L.; Johns Hopkins Childrens Center, Baltimore, Maryland and Flotte, Terence R., University of Florida, Gainesville, Florida; *A Phase I Study of an Adeno-associated Virus-CFTR Gene Vector in Adult CF Patients with Mild Lung Disease.* Sponsor: Targeted Genetics Corporation

*RAC Recommends Approval: 9-12-94/NIH Approval: 11-15-94

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9409-084 (Open) Gene Therapy/Phase I/Cancer/Breast/Antisense
In Vivo/Autologous Tumor Cells/Retrovirus/c-fos Antisense RNA/c-myc Antisense/Intrapleural/Intraperitoneal

Holt, Jeffrey, and Arteaga, Carlos B.; Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; *Gene Therapy for the Treatment of Metastatic Breast Cancer by In Vivo Infection with Breast-Targeted Retroviral Vectors Expressing Antisense c-fos or Antisense c-myc RNA.*

*RAC Recommends Approval: 9-12-94/NIH Approval: 1-4-95

9409-085 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Nasal Epithelial Cells/Respiratory Epithelial Cells/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intranasal/Respiratory Tract Administration (Bronchoscope)/Multiple Dose

Crystal, Ronald G.; New York Hospital-Cornell Medical Center, New York, New York; *Evaluation of Repeat Administration of a Replication Deficient, Recombinant Adenovirus Containing the Normal Cystic Fibrosis Transmembrane Conductance Regulator cDNA to the Airways of Individuals with Cystic Fibrosis.*

*RAC Recommends Approval: 9-12-94/NIH Approval: 11-30-94

9409-086 (Closed) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Avectin™/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Lyerly, H. Kim; Duke University Medical Center, Durham, North Carolina; *A Pilot Study of Autologous Human Interleukin-2 Gene Modified Tumor Cells in Patients with Refractory or Recurrent Metastatic Breast Cancer.*

*RAC Recommends Approval: 9-12-94/NIH Approval: 10-25-94

9409-087 (Open) Gene Therapy/Phase I/Monogenic Disease/Hunter Syndrome
In Vitro/Autologous Peripheral Blood Cells/Retrovirus/Iduronate-2-Sulfatase cDNA/Intravenous

Whitley, Chester B.; University of Minnesota, Minneapolis, Minnesota; *Retroviral-Mediated Transfer of the Iduronate-2-Sulfatase Gene into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II).*

*RAC Recommends Approval: 9-13-94/NIH Approval: 8-20-95

9409-088 (Closed) Gene Therapy/Phase I/Other/Peripheral Artery Disease
In Vivo/Vascular Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor cDNA/Intraarterial/Angioplasty Catheter/Hydrogel Coated Balloon

Isner, Jeffrey M. and Walsh, Kenneth; St. Elizabeth's Medical Center, Tufts University, Boston, Massachusetts; *Arterial Gene Transfer for Therapeutic Angiogenesis in Patients with Peripheral Artery Disease.*

*RAC Recommends Approval: 9-13-94/NIH Approval: 11-15-94
Follow-up has been completed: 11-29-01

9409-089 (Closed) Gene Therapy/Phase I/Cancer/Central Nervous System/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Stereotactic Injection

Eck, Stephen L. and Alavi, Jane B.; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Treatment of Advanced CNS Malignancy with the Recombinant Adenovirus H5.020RSVTK: A Phase I Trial.*

*RAC Recommends Approval: 9-13-94/NIH Approval: 2-2-96

9409-090 (Closed) Gene Therapy/Phase I/Cancer/n/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intrapleural

Albelda, Steven M.; University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Treatment of Advanced Mesothelioma with the Recombinant Adenovirus H5.010RSVTK: A Phase I Trial.*

*RAC Recommends Approval: 9-13-94/NIH Approval: 1-4-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9409-091 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Respiratory Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Respiratory Epithelial Cells/Bronchoscope

Dorkin, Henry L.; New England Medical Center, Tufts University, Boston, Massachusetts; and Lapey, Allen; Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; *Adenovirus Mediated Gene Transfer for Cystic Fibrosis: Safety of Single Administration in the Lung (lobar instillation).* Sponsor: Genzyme Corporation

NIH/ORDA Approval: 10-5-94 (Accelerated Review)
Protocol ended in December 1997

9411-092 (Closed) Gene Marking/Cancer/Lymphoma/Breast
In Vitro/CD34+ Autologous Bone Marrow Cells/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Douer, Dan; University of Southern California; Kenneth Norris Comprehensive Cancer Center and Hospital, Los Angeles, California; *High Dose Chemotherapy and Autologous Bone Marrow plus Peripheral Blood Stem Cell Transplantation for Patients with Lymphoma or Metastatic Breast Cancer: Use of Marker Genes to Investigate the Biology of Hematopoietic Reconstitution in Adults.*

NIH/ORDA Approval: 11-18-94 (Accelerated Review)

Notification that trial has been closed: 6-13-01

9411-093 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Subcutaneous Injection

Dranoff, Glen; Dana Farber Cancer Institute, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Irradiated Melanoma Cells Engineered to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.*

NIH/ORDA Approval: 11-23-94 (Accelerated Review)

Study closed, long-term follow-up continues: 7-16-01

9412-094 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis
In Vivo/Respiratory Epithelial Cells/Adenovirus/Serotype 2/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Respiratory Epithelial Cells/Aerosol Administration

Dorkin, Henry L.; New England Medical Center, Tufts University, Boston, Massachusetts; and Lapey, Allen; Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; *Adenovirus Mediated Gene Transfer for Cystic Fibrosis: Safety of a Single Administration in the Lung (aerosol administration).* Sponsor: Genzyme Corporation

*RAC Recommends Approval: 12-1-94/NIH Approval: 7-24-95
Protocol ended in December 1997

9412-095 (Closed) Gene Therapy/Phase I/Solid Tumors/Lymphoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1102/Cytokine/Interleukin-2 cDNA/Intratumoral/Direct Injection

Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; and Rinehart, John; Scott and White Clinic; Temple Texas. *Phase I Trial of Interleukin-2 Plasmid DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Solid Malignant Tumors or Lymphomas by Direct Gene Transfer.* Sponsor: Vical, Incorporated

*RAC Recommends Approval: 12-1-94/NIH Approval: 3-2-95

9412-096 (Closed) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral/Bronchoscope

Clayman, Gary; MD Anderson Cancer Center, Houston, Texas; *Clinical Protocol for Modification of Tumor Suppressor Gene Expression in Head and Neck Squamous Cell Carcinoma (HNSCC) with an Adenovirus Vector Expressing Wild-type p53.*

*RAC Recommends Approval: 12-2-94 and 9-11-95/NIH Approval: 9-21-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9412-097 (Open) Gene Therapy/Phase I/Cancer/Colon/Hepatic Metastases/Tumor Suppressor Gene In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intrahepatic/Hepatic Artery/Bolus Infusion

Venook, Alan and Warren, Robert; Moffitt-Long Hospital of the University of California, San Francisco Medical Center; *Gene Therapy of Primary and Metastatic Malignant Tumors of the Liver Using ACN53 Via Hepatic Artery Infusion: A Phase I Study.* Sponsor: Schering Plough Corporation (formerly Canji)

RAC Recommends Approval Contingent Upon Meeting Stipulations: 12-2-94

9412-098 (Open) Gene Therapy/Phase I/Cancer/Central Nervous System Malignancies/Pro-Drug In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intra- tumoral/Stereotactic Injection

Grossman, Robert and Woo, Savio; The Methodist Hospital, Houston, Texas; *Phase I Study of Adenoviral Vector Delivery of the HSV-TK Gene and the Intravenous Administration of Ganciclovir in Adults with Malignant Tumors of the Central Nervous System.*

*RAC Recommends Approval: 12-2-94/NIH Approval: 2-2-96

9502-099 (Open) Gene Therapy/Phase I/Cancer/Astrocytoma/Pro-Drug In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Stereotactic Injection

Fetell, Michael; Columbia Presbyterian Medical Center, New York, New York; Warnick, Ronald; University of Cincinnati, Cincinnati, OH; Yung, W.K. Alfred; M.D. Anderson Cancer Center, Houston, Texas; Maria, Bernard L.; University of Florida, Gainesville, Florida; Shaffrey, Mark; University of Virginia Health Sciences Center, Charlottesville, Virginia; Ram, Zvi; Chaim Sheba Medical Center, Tel Aviv University Sackler School of Medicine, Tel Hashomer, Israel; Prados, Michael; University of California, San Francisco, California; and Grossman, Stuart; Johns Hopkins University Hospital Oncology Center; Baltimore, Maryland; *Stereotactic Injection of Herpes Simplex Thymidine Kinase Vector Producer Cells (PA317/G1TkSvNa.7) and Intravenous Ganciclovir for the Treatment of Recurrent Malignant Glioma.* Sponsor: Genetic Therapy, Inc./Novartis

NIH/ORDA Approval: 2-10-95 (Accelerated Review)

9503-100 (Closed) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraperitoneal/Catheter

Link, Charles; Human Gene Therapy Research Institute; and Moorman, Donald; Iowa Methodist Medical Center, Des Moines, Iowa; *A Phase I Trial of In Vivo Gene Therapy with Herpes Simplex Thymidine Kinase/Ganciclovir System for the Treatment of Refractory or Recurrent Ovarian Cancer.*
*RAC Recommends Approval: 3-6-95/NIH Approval: 7-27-95

9503-101 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-7 cDNA/Hygromycin Phosphotransferase/Herpes Simplex Virus Thymidine Kinase cDNA/Subcutaneous Injection

Economou, James; Glaspy, John; and McBride, William; University of California, Los Angeles, California; *A Phase I Testing of Genetically Engineered Interleukin-7 Melanoma Vaccines.*

*RAC Recommends Approval: 3-6-95/NIH Approval: 8-20-95
Closed: 3-97

9503-102 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy In Vitro/HLA-Matched Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-2 cDNA/Gamma Interferon cDNA/Subcutaneous Injection

Gansbacher, Bernd; Memorial Sloan Kettering Cancer Center, New York, New York; *Phase I/II Study of Immunization with MHC Class I Matched Allogeneic Human Prostatic Carcinoma Cells Engineered to Secrete Interleukin-2 and Interferon-γ.*

RAC Recommends Approval Contingent Upon Meeting Stipulations: 3-6-95

9503-103 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense In Vitro/Antisense TAR/Transdominant Rev/Intravenous

Tavel, Jorge; National Institutes of Health, Bethesda, Maryland; *Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins.*

*RAC Recommends Approval: 3-7-95/NIH Approval: 4-1-95
Closed to new enrollment. Individuals will be followed, long-term, in a new protocol (that does not involve administration of recombinant DNA): 1-17-02

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9503-104 (Open) Gene Therapy/Phase I/Monogenic Disease/Chronic Granulomatous Disease
In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/p47phox/Intravenous

Malech, Harry; National Institutes of Health, Bethesda, Maryland; *Gene Therapy Approach for Chronic Granulomatous Disease.*

*RAC Recommends Approval: 3-7-95/NIH Approval: 4-15-95

9503-105 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy
In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Parenti, David; George Washington University Medical Center, Washington, D.C.; Haubrich, Richard; University of California San Diego Treatment Center, San Diego, California; Frame, Peter; University of Cincinnati AIDS Treatment Center, Cincinnati, Ohio; Powderly, William; Washington University AIDS Clinical Trials Unit; St. Louis, Missouri; and Loveless, Mark; Oregon Health Sciences University, Portland, Oregon; *A Repeat Dose Safety and Efficacy Study of HIV-IT(V) in HIV-1 Infected Subjects with Greater Than or Equal to 100 CD4+ T Cells and No AIDS Defining Symptoms.*

NIH/ORDA Approval: 3-11-95 (Accelerated Review)

Notification that trial has been completed, IND is inactive: 5-22-00

9506-106 (Open) Gene Marking/Cancer/Chronic Myelogenous Leukemia
In Vitro/Autologous G-CSF and ATA-C Mobilized Bone Marrow Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Verfaillie, Catherine; University of Minnesota, Minneapolis, Minnesota; *Autologous Marrow Transplantation for Chronic Myelogenous Leukemia Using Stem Cells Obtained After In Vivo Chemotherapy Cytokine Priming.*

NIH/ORDA Approval: 5-5-95

9506-107 (Open) Gene Therapy/Phase I/Cancer/Multiple Myeloma/Pro-Drug
In Vitro/Allogeneic T Lymphocytes/Retrovirus/Herpes Simplex Thymidine Kinase/Ganciclovir/Intravenous

Munshi, Nikhil C. and Barlogie, Bart; University of Arkansas for Medical Sciences, Little Rock, Arkansas; *Thymidine Kinase (TK) Transduced Donor Leukocyte Infusions as a Treatment for Patients with Relapsed or Persistent Multiple Myeloma after T-cell Depleted Allogeneic Bone Marrow Transplant.*
Sponsor: Genetic Therapy, Inc./Novartis

*RAC Recommends Approval: 6-9-95/NIH Approval: 7-27-95

9506-108 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Melanoma/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Subcutaneous Injection

Fox, Bernard A. and Urba, Walter J.; Earle A. Chiles Research Institute, Providence Medical Center, Portland, Oregon; *Adoptive Cellular Therapy of Cancer Combining Direct HA-B7/β-2 Microglobulin Gene Transfer with Autologous Tumor Vaccination for the Generation of Vaccine-Primed Anti-CD3 Activated Lymphocytes.*

*RAC Recommends Approval: 6-9-95/NIH Approval: 9-30-95

9506-109 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Immunotherapy
In Vitro/Anti-CD3 Stimulated Autologous Peripheral Blood Lymphocytes/Retrovirus/Antibody/MOv-gamma (Reactive with Folate Binding Protein)/Intravenous/Intraperitoneal

Hwu, Patrick; National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Advanced Epithelial Ovarian Cancer using Anti-CD3 Stimulated Peripheral Blood Lymphocytes Transduced with a Gene Encoding a Chimeric T-cell Receptor Reactive with Folate Binding Protein.*

RAC Recommends Approval Contingent Upon Meeting Stipulations: 6-9-95

9506-110 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Immunotherapy
In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/DDAB-DOPE/Cytokine/Interleukin-2 cDNA/Intradermal Injection

Berchuck, Andres and Lyerly, H. Kim; Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Autologous Human Interleukin-2 (IL-2) Gene Modified Tumor Cells in Patients with Refractory Metastatic Ovarian Cancer.*

*RAC Recommends Approval: 6-10-95/NIH Approval: 9-30-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9506-111 (Closed) Gene Therapy/Phase I/Monogenic Disease/Purine Nucleoside Phosphorylase Deficiency In Vitro/Autologous Peripheral Blood Lymphocytes/Retrovirus/Purine Nucleoside Phosphorylase cDNA/Intravenous

McIvor, R. Scott; Institute of Human Genetics, University of Minnesota, Minneapolis, Minnesota; *Gene Therapy for Purine Nucleoside Phosphorylase Deficiency.*

*RAC Recommends Approval: 6-9-95/NIH Approval: 7-27-95
Closed: 9-24-00 No individuals enrolled, IND not submitted

9506-112 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Single Chain Antibody Gene/In Vitro/CD4+ Autologous Peripheral Blood Lymphocytes/Retrovirus/sFv105 Anti-HIV-1 Envelope Protein(gp160)Gene/Intravenous

Marasco, Wayne A.; Dana Farber Cancer Institute, Boston, Massachusetts; *Intracellular Antibodies Against HIV-1 Envelope Protein for AIDS Gene Therapy.*
*RAC Recommends Approval: 6-9-95/NIH Approval: 7-27-95

9504-113 (Closed) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus-1/Immunotherapy In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1IIIB Envelope Protein/Intramuscular Injection

Conant, Marcus, Conant Medical Group; Lang, William, ViRx, Inc.; and Merritt, James, Viagene, Inc., San Francisco, California; *A Randomized, Double Blinded, Phase I/II Dosing Study to Evaluate the Safety and Optimal CTL Inducing Dose of HIV-IT(V) in Pre-Selected HIV-1 Infected Subjects.*

*RAC Recommends Approval: NA/NIH Approval: NA (Non-NIH funded institution)
FDA Approval: 5-6-94

9507-114 (Open) Gene Therapy/Phase I-II/Monogenic Disease/Cystic Fibrosis In Vivo/Maxillary Sinus Epithelial Cells/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Maxillary Sinus Administration

Gardner, Phyllis; Stanford University School of Medicine, Stanford, California; *A Phase I/II Study of tg-CF for the Treatment of Chronic Sinusitis in Patients with Cystic Fibrosis.* Sponsor: Targeted Genetics Corporation

Sole FDA Review Recommended by NIH/ORDA: 7-11-95

9508-115 (Closed) Gene Therapy/Phase II/Cancer/Metastatic Malignancies(Breast Adenocarcinoma, Renal Cell Carcinoma, Melanoma, Colorectal Adenocarcinoma, non-Hodgkin's Lymphoma)/Immunotherapy In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Chang, Alfred E.; University of Michigan Medical Center, Ann Arbor, Michigan; Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; Vogelzang, Nicholas; University of Chicago Medical Center, Chicago, Illinois; Levy, Ronald; Stanford University Medical Center, Palo Alto, California; Redman, Bruce; Wayne State University School of Medicine; Detroit, Michigan; Figlin, Robert; University of California Medical Center, Los Angeles, California; Rubin, Joseph; Mayo Foundation for Medical Evaluation and Research, Rochester, Minnesota; Rinehart, John J.; Scott and White Hospital, Texas A & M University, Temple Texas; Doroshow, James H.; City of Hope National Medical Center, Duarte, California; Klasa, Richard; British Columbia Cancer Agency, Vancouver, British Columbia; Sobol, Robert; Sidney Kimmel Cancer Center, San Diego, California; *Phase II Study of Immunotherapy of Metastatic Cancer by Direct Gene Transfer.* Sponsor: Vical, Incorporated

Sole FDA Review Recommended by NIH/ORDA: 8-2-95

9508-116 (Open) Gene Therapy/Phase I/Cancer/Glioma/Immunotherapy In Vitro/Autologous Tumor (Glioma) Cells/Non-Irradiated/Retrovirus/Cytokine/Interleukin-4 cDNA/Subcutaneous Injection

Pollack, Ian; Okada, Hideho; and Lotze, Michael T.; University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; *Gene Therapy of Malignant Gliomas: A Phase I Study of IL-4 Gene -Modified Autologous Tumor to Elicit an Immune Response.*

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-117 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition In Vitro/Autologous CD34+ Peripheral Blood Cells/Retrovirus/Hammerhead Ribozyme/Intravenous

Mitsuyasu, Ronald; University of California Los Angeles, California; *A Phase I Trial of Autologous CD34+ Hematopoietic Progenitor Cells Transduced with an Anti-HIV-1 Ribozyme.*

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9508-118 (Open) Gene Therapy/Phase I/Other/Restenosis
In Vivo/Vascular Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor cDNA/Intraarterial/Angioplasty Catheter/Hydrogel Coated Balloon

Losordo, Douglas W.; St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts; *Accelerated Re-endothelialization and Reduced Neointimal Thickening Following Catheter Transfer of phVEGF165.*

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-119 (Open) Gene Therapy/Phase I/Human Immunodeficiency Virus-1
In Vitro/CD8+ Allogeneic Cytotoxic T Lymphocytes/CD8+ Syngeneic Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase/Herpes Simplex Virus Thymidine Kinase cDNA/Retrovirus/Intravenous

Riddell, Stanley R.; Fred Hutchinson Cancer Research Center, Seattle, Washington; *Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy using Autologous Unmodified and Genetically Modified CD8+ HIV-Specific T Cells in HIV Seropositive Individuals.* Sponsor: Targeted Genetics Corporation

Sole FDA Review Recommended by NIH/ORDA: 8-7-95

9508-120 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Used to Derive Tumor Infiltrating Lymphocytes/HLA-B7 cDNA/Intravenous

Chang, Alfred E. and Nabel, Gary J.; University of Michigan Medical Center, Ann Arbor, Michigan; *Phase I Study of Tumor-Infiltrating Lymphocytes Derived from In Vivo HLA-B7 Gene Modified Tumors in the Adoptive Immunotherapy of Melanoma.*

Sole FDA Review Recommended by NIH/ORDA: 8-14-95

9508-121 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell/Immunotherapy
In Vivo/Autologous Tumor Cells/HLA B7 cDNA/Intratumoral/Concurrent Interleukin-2 Therapy

Figlin, Robert A.; University of California Los Angeles Medical Center, Los Angeles, California; *Phase I Study of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Renal Cell Carcinoma by Direct Gene Transfer with Concurrent Low Dose Bolus IL-2 Protein Therapy.* Sponsor: Vical, Incorporated

Sole FDA Review Recommended by NIH/ORDA: 8-14-95

9508-122 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies (type of cancer not specified)/Immunotherapy
In Vivo/Autologous Muscle Cells/Canarypox Virus/Carcinoembryonic Antigen cDNA/Intramuscular Injection

Hawkins, Michael J. and Marshall, John L.; Georgetown University Medical Center, Washington, D.C.; *A Study of Recombinant ALVAC Virus that Expresses Carcinoembryonic Antigen in Patients with Advanced Cancers.*

Sole FDA Review Recommended by NIH/ORDA 8-14-95

9509-123 (Open) Gene Therapy/Phase I/Cancer/Prostate/Antisense
In Vivo/Autologous Tumor Cells/Retrovirus/Antisense c-myc RNA/Intraprostate Injection

Steiner, Mitchell S., Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; and Holt, Jeffrey T., Vanderbilt University School of Medicine, Nashville, Tennessee; *Gene Therapy for the Treatment of Advanced Prostate Cancer by In Vivo Transduction with Prostate-Targeted Retroviral Vectors Expressing Antisense c-myc RNA.*

*RAC Recommends Approval: 9-11-95/NIH Approval: 9-30-95

9509-124 (Open) Gene Therapy/Phase I/Cancer/Ovarian and Extraovarian/Anti-erbB-2 Single Chain Antibody Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Anti-erbB-2 (oncoprotein/extracellular domain) Single-chain Antibody Gene/Intraperitoneal Injection

Curiel, David T. and Alvarez, Ronald D.; University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Study of Recombinant Adenovirus Vector-Mediated Delivery of an Anti-erbB-2 Single Chain (sFv) Antibody Gene for Previously Treated Ovarian and Extraovarian Cancer Patients.*

RAC Recommends Approval Contingent Upon Meeting Stipulations: 9-11-95

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9509-125 (Closed) Gene Therapy/Phase I/Cancer/Colon Carcinoma (Hepatic Metastases)/Pro-Drug In Vivo/Autologous Tumor Cells/Adenovirus/E. coli Cytosine Deaminase cDNA/Intratumoral (Hepatic) Injection/Combined with Oral 5-Fluorocytosine

Crystal, Ronald, G.; Hershowitz, Edward; and Lieberman, Michael; New York Hospital-Cornell Medical Center, New York, New York; *A Phase I Study of Direct Administration of a Replication-Deficient Adenovirus Vector Containing the E. coli Cytosine Deaminase Gene to Metastatic Colon Carcinoma of the Liver in Association with the Oral Administration of the Pro-Drug 5-Fluorocytosine.*

*RAC Recommends Approval: 9-11-95/NIH Approval: 9-30-95
Notification that IND has been withdrawn: 2-2-00

9509-126 (Open) Gene Therapy/Phase I/Cancer/Prostate Adenocarcinoma/Immunotherapy In Vivo/Vaccination/Vaccinia Virus/Prostate Specific Antigen/Intradermal Injection

Chen, A.P.; National Naval Medical Center, Bethesda, Maryland; *A Phase I Study of Recombinant Vaccinia that Expresses Prostate Specific Antigen in Adult Patients with Adenocarcinoma of the Prostate.*

Sole FDA Review Recommended by NIH/ORDA: 9-22-95

9509-127 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis In Vivo/Nasal Epithelial Cells/Cationic Liposome Complex/DOPE/Cystic Fibrosis Transmembrane Conductance Regulator cDNA; Intranasal Administration

Welsh, Michael J. and Zabner, Joseph; Howard Hughes Medical Institute, University of Iowa College of Medicine, Iowa City, Iowa; *Cationic Lipid Mediated Gene Transfer of CFTR: Safety of a Single Administration to the Nasal Epithelia.* Sponsor: Genzyme Corporation

Sole FDA Review Recommended by NIH/ORDA: 9-26-95

9510-128 (Open) Gene Therapy/Phase I/Cancer/Gastrointestinal Tract, Breast, or Lung Adenocarcinoma (CEA-Expressing Malignancies)/Immunotherapy/In Vivo/Vaccination/Vaccinia Virus/Carcinoembryonic Antigen/Intradermal Injection in Combination with Subcutaneous Peptide Challenge

Cole, David J.; Medical University of South Carolina, Charleston, South Carolina; *Phase I Study of Recombinant CEA Vaccinia Virus Vaccine with Post Vaccination CEA Peptide Challenge.*

Sole FDA Review Recommended by NIH/ORDA: 10-16-95

9510-129 (Open) Gene Marking/Cancer/EBV-Positive Hodgkin Disease In Vitro/EBV-Specific Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Roskrow, Marie; Hudson, Melissa; Rooney, Cliona; Heslop, Helen; and Brenner, Malcolm; St. Jude Children's Research Hospital, Memphis, Tennessee; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes as Therapy for Patients Receiving a Bone Marrow Transplant for Relapsed EBV-Positive Hodgkin Disease.*

Sole FDA Review Recommended by NIH/ORDA: 10-17-95

9510-130 (Open) Gene Marking/Cancer/EBV-Positive Hodgkin Disease In Vitro/EBV-Specific Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Administration

Roskrow, Marie; Hudson, Melissa; Rooney, Cliona; Heslop, Helen; and Brenner, Malcolm; St. Jude Children's Research Hospital, Memphis, Tennessee; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin Disease.*

Sole FDA Review Recommended by NIH/ORDA: 10-17-95

9510-131 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus In Vitro/Autologous CD8+ T Cells/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous

Connick, Elizabeth; University of Colorado Health Sciences Center, Denver, Colorado; and Deeks, Steven G.; University of California, San Francisco General Hospital, San Francisco, California; *A Randomized, Controlled, Phase II Study of the Activity and Safety of Autologous CD4-Zeta Gene-Modified T Cells in HIV-Infected Patients.* Sponsor: Cell Genesys, Inc.

Sole FDA Review Recommended by NIH/ORDA: 10-17-95
Closed 8-6-97 (No longer enrolling patients)

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9510-132 (Open) Gene Therapy/Phase I/Cancer/Locally Advanced or Metastatic Prostate/Immunotherapy In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Cytokine/Interleukin-2 cDNA/Intradermal Injection

Paulson, David; and Lyerly, H. Kim; Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Autologous Human Interleukin-2 (IL-2) Gene Modified Tumor Cells in Patients with locally Advanced or Metastatic Prostate Cancer.*

Sole FDA Review Recommended by NIH/ORDA: 10-19-95

9511-133 (Closed) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy In Vitro/Autologous Tumor Cells (Non-irradiated)/Type 5 Adenovirus/Cytokine/Interleukin-2 cDNA/Subcutaneous Injection

Brenner, Malcolm K.; Dilloo, Dagmar; and Bowman, Laura; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9511-134 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition In Vitro/Autologous CD4+ T Cells/Retrovirus/Neomycin Phosphotransferase Gene/PolyTAR Decoy Gene/RRE-polyTAR Decoy Gene

Greenberg, Philip D.; Fred Hutchinson Cancer Research Center, University of Washington Medical Center, Seattle, Washington; *Phase I Study to Evaluate the Safety and In Vivo Persistence of Adoptively Transferred Autologous CD4+ T Cells Genetically Modified to Resist HIV Replication.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

Trial is closed to new accrual; follow-up will continue: 03-19-01

9511-135 (Open) Gene Therapy/Phase I/Cancer/Ovarian and Extraovarian Cancer/Single Chain Antibody In Vivo/Autologous Tumor Cells/Adenovirus/Herpes Simplex Thymidine Kinase Gene/Intraperitoneal Injection/Combined with Intravenous Ganciclovir Administration

Alvarez, Ronald D. and Curiel, David T.; University of Alabama Comprehensive Cancer Center, Birmingham, Alabama; *A Phase I Study of Recombinant Adenovirus Vector-Mediated Intraperitoneal Delivery of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Gene and Intravenous Ganciclovir for Previously Treated Ovarian and Extraovarian Cancer Patients.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9511-136 (Open) Gene Therapy/Phase I/Cancer/Metastatic Melanoma/Immunotherapy In Vitro/Autologous CD8+ Tyrosinase-Specific TCells/Retrovirus/Hygromycin Phosphotransferase/Intravenous Administration

Yee, Cassian and Greenberg, Philip D.; Fred Hutchinson Cancer Research Center, University of Washington Medical Center, Seattle, Washington; *Phase I Study to Evaluate the Safety of Cellular Adoptive Immunotherapy Using Autologous Unmodified and Genetically Modified CD8+ Tyrosinase-Specific T Cells in Patients with Metastatic Melanoma.*

Sole FDA Review Recommended by NIH/ORDA: 11-1-95

9512-137 (Open) Gene Therapy/Phase I/Cancer/Ovarian,Breast/Oncogene Regulation/HER-2/*neu* In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intraperitoneal, Intrapleural Administration

Hortobagyi, Gabriel N.; Lopez-Berstein, Gabriel; and Hung, Mien-Chien; MD Anderson Cancer Center, Houston, Texas; Kilbourn, Robert, Rush-Presbyterian/St. Luke's Medical Center, Chicago, Illinois; Weiden, Paul; Virginia Mason Medical Center, Seattle, Washington; *Phase I Study of E1A Gene Therapy for Patients with Metastatic Breast or Ovarian Cancer that Overexpresses Her-2/neu.* Sponsor: Targeted Genetics Corporation

*RAC Recommends Approval: 12-4-95/NIH Approval: 2-2-96

9512-138 (Open) Gene Therapy/Phase I/Cancer/Malignant Glioma/Antisense In Vitro/Autologous Tumor Cells/Lethally Irradiated/Plasmid DNA--Electroporation/TGF-β2/Subcutaneous Injection

Black, Keith L.; and Fakhrai, Habib; University of California, Los Angeles, School of Medicine, Los Angeles, California; *A Phase I Study of the Safety of Injecting Malignant Glioma Patients with Irradiated TGF-β2 Antisense Gene Modified Autologous Tumor Cells.*

*RAC Recommends Approval: 12-4-95/NIH Approval: 4-2-96

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9512-139 (Open) Gene Therapy/Phase I/Monogenic Disease/Partial Ornithine Transcarbamylase (OTC) Deficiency
In Vivo/Autologous Peripheral Blood Cells/Adenovirus/Type 5 (E2a Temperature-Sensitive Mutant)/Ornithine Transcarbamylase cDNA/Intravenous

Batshaw, Mark; Institute for Human Gene Therapy, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *A Phase I Study of Adenoviral Vector Mediated Gene Transfer to Liver in Adults with Partial Ornithine Transcarbamylase Deficiency.*

RAC Recommends Approval Contingent Upon Meeting Stipulations: 12-4-95

9512-140 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/
In Vivo/Adenovirus/Type 2/MART-1 Melanoma Antigen/Subcutaneous Injection/Immunization

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the MART-1 Melanoma Antigen.*

Sole FDA Review Recommended by NIH/ORDA: 12-1-95

9512-141 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition
In Vitro/Autologous CD4+ Peripheral Blood Lymphocytes/Retrovirus/Anti-Rev SFv/Intravenous

Pomerantz, Roger J; Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania; *Intracellular Immunization Against HIV-1 Infection Using an Anti-Rev Single Chain Variable Fragment (SFv).*

Sole FDA Review Recommended by NIH/ORDA: 12-13-95

9512-142 (Open) Gene Therapy/Phase I/Gene Therapy/Cancer/Head and Neck Squamous Cell Carcinoma/Immunotherapy
In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Gluckman, Jack L.; University of Cincinnati Medical Center, Cincinnati, Ohio; *Allovectin-7 in the Treatment of Squamous Cell Carcinoma of the Head and Neck.*

Sole FDA Review Recommended by NIH/ORDA: 12-15-95

9601-143 (Closed) Gene Therapy/Phase I/Cancer/Breast/Chemoprotection
In Vitro/Autologous CD34+ Peripheral Blood Lymphocytes//Retrovirus/Multi-Drug Resistance-1 cDNA/Neomycin Phosphotransferase cDNA/Intravenous

Cowan, Kenneth H.; National Institutes of Health, Bethesda, Maryland; *Antimetabolite Induction, High-Dose Alkylating Agent Consolidation, and Retroviral Transduction of the MDR1 Gene Into Peripheral Blood Progenitor Cells Followed by Intensification Therapy with Sequential Paclitaxel and Doxorubicin for Stage 4 Breast Cancer.*

Sole FDA Review Recommended by NIH/ORDA: 1-26-96
Closed: 6-14-00

9601-144 (Open) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Intra-prostatic Tumor Injection

Scardino, Peter T.; Thompson, TImothy C.; and Woo, Savio L.C.; Baylor College of Medicine, Houston, Texas; *Phase I Study of Adenoviral Vector Delivery of the HSV-tk Gene and the Intravenous Administration of Ganciclovir in Men with Local Recurrence of Prostate Cancer after Radiation Therapy.*

Sole FDA Review Recommended by NIH/ORDA: 1-29-96

9601-145 (Closed) Gene Therapy/Phase I/Cancer/Bladder/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Retinoblastoma cDNA/Intravesical Catheter Administration

Small, Eric J. and Carroll, Peter R.; University of California, San Francisco, California; *Gene Therapy of Bladder Cancer Using Recombinant Adenovirus Containing the Retinoblastoma Gene (ACNRB): A Phase IA Study.* Sponsor: Schering Plough Corporation (formerly Canji)

Sole FDA Review Recommended by NIH/ORDA: 1-30-96
Canceled: 4-4-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9602-146 (Open) Gene Therapy/Phase I/Cancer/Hematologic Malignancies Following Allogeneic Bone Marrow Transplant/Pro-Drug/Elimination of Graft Versus Host Disease
In Vitro/Allogeneic Peripheral Blood Lymphocytes/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intravenous

Link, Charles J.; Human Gene Therapy Research Institute, Des Moines, Iowa; Burt, Richard K. and Traynor, Ann; Northwestern University School of Medicine, Chicago, Illinois; *Adoptive Immunotherapy for Leukemia: Donor Lymphocytes Transduced with the Herpes Simplex Thymidine Kinase Gene for Remission Induction.*

Sole FDA Review Recommended by NIH/ORDA: 2-8-96

9602-147 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense
In Vitro/CD34+ Autologous Bone Marrow Cells/Retrovirus/RRE Decoy Gene, and Retrovirus/Neomycin Phosphotransferase Gene/Intravenous

Kohn, Donald B.; Childrens Hospital Los Angeles, Los Angeles, California; *Transduction of CD34+ Cells from the Bone Marrow of HIV-1 Infected Children: Comparative Marking by an RRE Decoy and a Neutral Gene.*

Sole FDA Review Recommended by NIH/ORDA: 2-8-96

9602-148 (Open) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell Carcinoma/Pro-Drug
In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

O'Malley, Bert W.; Johns Hopkins University, Baltimore, Maryland; *Phase I Study of Adenoviral Vector Delivery of the HSV-tk Gene and the Intravenous Administration of Ganciclovir in Adults with Recurrent or Persistent Head and Neck Cancer.*

Sole FDA Review Recommended by NIH/ORDA: 2-13-96

9603-149 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Tumor Suppressor Gene
In Vivo/Autologous Tumor Cells/Retrovirus/BRCA-1 Gene/Intraperitoneal Administration (Ultrasound Guided)

Holt, Jeffrey T.; Clinical Research Center at Vanderbilt University Medical Center, Nashville, Tennessee; *Ovarian Cancer Gene Therapy with BRCA-1.*

Sole FDA Review Recommended by NIH/ORDA: 3-6-96

9603-150 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy In Vivo/Autologous Tumor Cells/HLA B7 cDNA/Intratumoral/Concurrent Interleukin-2 Therapy

Hersh, Evan M.; Arizona Cancer Center, Tucson, Arizona; and Sondak, Vernon K.; University of Michigan Medical Center, Ann Arbor, Michigan; *Evaluation of Intratumoral Gene Therapy with HLA-B7/DMRIE/DOPE plus Subcutaneous Low Dose Il-2.*

Sole FDA Review Recommended by NIH/ORDA; 3-26-96

Closed: 3-11-97. Protocol Never Initiated

9604-151 (Closed) Gene Therapy/Phase I/ Cancer/Melanoma/Immunotherapy In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 2/GP100 Melanoma Antigen/Subcutaneous or Intramuscular Injection/Concurrent Interleukin-2 Therapy

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Adenovirus Encoding the GP100 Melanoma Antigen.*

Sole FDA Review Recommended by NIH/ORDA: 4-19-96

9604-152 (Open) Gene Therapy/Phase I/Inherited Genetic Disorder/Monogenic Disease/X-Linked Severe Combined Immune Deficiency/Correction In Vitro/CD34+ Autologous Umbilical Cord Blood or Bone Marrow/Retrovirus/cDNA for Common γ Chain of Multiple Cytokine Receptors/Intravenous

Weinberg, Kenneth I.; Childrens Hospital Los Angeles (CHLA) ; Los Angeles, California; *Gene Therapy for X-linked Severe Combined Immune Deficiency using Retroviral Mediated Transduction of the γc cDNA into CD34+ Cells.*

Sole FDA Review Recommended by NIH/ORDA: 4-24-96

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9604-153 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Hammerhead Ribozyme/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Tat and Rev Hammerhead Ribozyme/Intravenous

Kohn, Donald B.; Childrens Hospital of Los Angeles (CHLA), Los Angeles, California; and Zaia, John A.; City of Hope National Medical Center, Duarte, California; *Transduction of CD34+ Autologous Peripheral Blood Progenitor Cells from HIV-1 Infected Persons: a Phase I Study of Comparative Marking Using a Ribozyme Gene and a Neutral Gene.*

Sole FDA Review Recommended by NIH/ORDA: 4-24-96

9605-154 (Closed) Gene Therapy/Phase I/Cancer/Brain Tumors/Pro-Drug/In Vivo/Autologous Tumor Cells/psiCRIP-MFG-S-TK1-67 Cells/Retrovirus/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Harsh IV, Griffith R.; Chiocca, E. Antonio; and Hochberg, Fred H.; Harvard Medical School, Boston, Massachusetts; *Phase I Study of Retroviral-Mediated Incorporation of the HSV Thymidine Kinase Gene and Ganciclovir in Malignant Gliomas.*

Sole FDA Review Recommended by NIH/ORDA: 5-1-96

9605-155 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Cationic Liposome Complex/B7(CD80) cDNA/Retrovirus/Herpes Simplex Thymidine Kinase/Ganciclovir/Intraperitoneal

Freeman, Scott M.; and Robinson III, William R.; Tulane University School of Medicine, New Orleans, Louisiana; *Tumor Vaccination With HER-2/Neu Using a B7 Expressing Tumor Cell Line Prior To Treatment With HSV-TK Gene-Modified Cells.*

Sole FDA Review Recommended by NIH/ORDA: 5-2-96

9608-156 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/B7(CD80) cDNA/Subcutaneous Injection

Urba, Walter J.; Providence Portland Medical Center, Portland, Oregon; *Phase I Trial Using a CD80-Modified Allogeneic Breast Cancer Line to Vaccinate HLA-A2-Positive Women with Breast Cancer .*

Sole FDA Review Recommended by NIH/ORDA: 8-6-96

9608-157 (Closed) Gene Therapy/Phase III of #9303-037/Cancer/Glioblastoma/Pro-Drug/In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Maria, Bernard; University of Florida, Gainsville, Florida; Gutheil, John; Sharp Healthcare, Sidney Kimmel Cancer Center, San Diego, California; Bucholz, Richard; St. Louis University, St. Louis, Missouri; Olson, Jeffrey; Emory School of Medicine, Winship Cancer Center, Atlanta, Georgia; Lillehei, Kevin; University of Colorado, Denver, Colorado; Van Gilder, John; University of Iowa College of Medicine, Iowa City, Iowa; Nemunaitis, John; Texas Oncology P.A., Baylor University Medical Center, Dallas, Texas; Origitano, Thomas; Loyola University Medical Center, Maywood, Illinois; Warnick, Ronald; University of Cincinnati Medical Center, The Christ Hospital, Good Samaritan Hospital, Jewish Hospital of Cincinnati, Veterans Affairs Medical Center, Cincinnati, Ohio; Weber, Friederich Dr. med.; Heinrich Heine Universtat, Dusseldorf, Germany; Rainov, Nikolai, PD Dr. med.; Martin Luther Universtat, Halle, Germany; Cloughesy, Timothy; UCLA Department of Neurology, Reed Neurological Research Center, Boywer Oncology Clinic, Los Angeles, California; Markert, James; University of Alabama at Birmingham, Birmingham, Alabama; Matti Vapalahti, Kuopio Universiy Hopsital, Kuopio, Finland; Yasuhiro Yonekawa, University Hospital, Zurich, Switzerland; Nanno Harrie Mulder, Academic Hospital Groningen, Groningen, The Netherlands; Susanne Osante, Academic Hospital Leiden, Leiden, The Netherlands; Fetell, Michael; Columbia-Presbyterian Medical Center Neurological Institute, New York, New York; Schramm, Johannes; Prof. Dr. med., Univ. Klinikum Neurochirurgische Klinik, Bonn, Germany; Westphal, Manfred, PD Dr. med.; Klinikum Eppendorf Neurochirurgie/Univ. Martinstr. 52, Hamburg, Germany; Tonn, Jorg-Christian, PD Dr. med.; u. Poliklinik/Univ. Kliniken, Wurzberg, Germany; Moumdjian, Robert, Dr.; Hospital Notre-Dame, Montreal, Quebec, Canada; Shaffrey, Mark; University of Virginia, Charlottesville, Virginia; Asher, Anthony; Presbyterian Hospital, Cancer Center, Charlotte, North Carolina; Epstein, Mel; Brown University, Providence, Rhode Island; Schmidt-Schackert, Frau.Prof. Dr. med.; Gabriele, Univ.-Klin. Kar-G. Carus, Klinik f. Neurochirurgie, Dresden, Germany; Mendez, Ivar; Victoria General Hospital, Halifax, Nova Scotia, Canada; Bernstein, Mark, The Toronto Hospital, Toronto, Ontario, Canada; Quigley, Mathew, Alleghemy University of Health Sciences, Pittsburgh, Pennsylvania; Payner, Troy; Indianapolis Surgical Group, Indianapolis, Indiana; Kulvik, Martti; Helsinki University Central Hospital, Helsinki, Finland; Seiler, Rolf W.; University Hospital, Bern, Switzerland; Weiss, Martin Harvey; University of Southern California, Department of Neurosurgery, Los Angeles, California; Fick, James R.; Medical College of Georgia, Department of Surgery, Augusta, Georgia; Leblanc, Richand; Montreal Neurological Institute, Montreal, Quebec, Canada; Buchfelder, Michael; Neurochirurgische Klinik mit Poliklinik der Universtat Erlangen-Nurnberg, Erlangen, Germany; Brotchi, Jacques; Hopital Erasme, Neruosergery, Cliniques Universiaites de Bruxelles, Bruxelles, Belgium; Astrup, Jens; Arhus Kommunehospital, Arhus C, Denmark; Henriksson, Roger; University Hospital, Umea, Sweden; Maciunas, Robert J.; Vanderbilt University Medical Center, Nashville, Tennessee; Ram, Zvi; The Chaim Sheba Medical Center; Tel-Hashomer, Israel; Andrews, David; Thomas Jefferson University Hospita, Philadelphia, Pennsylvania; Verlooy, Jan; University Hospital Antwerp; Antwerp, Belgium; Stockhammer, Gunther; Universitatsklinik fur Neurologie, Innsbruck, Austria; Favrot, Marie; Centre Leon Berard, Lyon, France; and Finocchiaro, Gaetano; Unita Neuroncologia Molecolare e Terapia Genica, Istituto Nazionale Neurologico Carlo Besta, Milano Mi Italy; *Prospective, Open-Label, Parallel-Group, Randomized Multicenter Trial Comparing the Efficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previously Untreated Glioblastoma.* Sponsor: Genetic Therapy, Inc./Novartis

Sole FDA Review Recommended by NIH/ORDA: 8-22-96

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9608-158 (Open) Gene Therapy/Phase I-IB/Cancer/Melanoma or Sarcoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Plasmid DNA/Particle Mediated Gene Transfer (Accell®)/Cytokine/GM-CSF cDNA/Subcutaneous Injection

Mahvi, David M.; University of Wisconsin Hospital and Clinics Comprehensive Cancer Center, Madison, Wisconsin; *Phase I/IB Study of Immunization with Autologous Tumor Cells Transfected with the GM-CSF Gene by Particle-Mediated Transfer in Patients with Melanoma or Sarcoma.*

Sole FDA Review Recommended by NIH/ORDA: 8-26-96

9605-159 (Open) Gene Marking/Cancer/Pediatric Malignancies/In Vitro/CD34+ Autologous Bone Marrow and Peripheral Blood/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplant

Heslop, Helen E.; Brenner, Malcolm K.; Krance, Robert A.; Baylor College of Medicine, Houston, Texas; *A Comparative Evaluation of the Utility of Hemopoietic Progenitor Cells Derived from Peripheral Blood vs Bone Marrow.*

Sole FDA Review Recommended by NIH/ORDA: 5-15-96

9609-160 (Open) Gene Therapy/Phase I/Cancer/Prostate Adenocarcinoma/Immunotherapy/In Vivo/Vaccination/Vaccinia Virus/Prostate Specific Antigen/Intradermal Injection

Kufe, Donald W.; and Eder, Joseph Paul; Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Trial Of Recombinant Vaccinia Virus That Expresses PSA In Patients With Adenocarcinoma Of The Prostate.*

Sole FDA Review Recommended by NIH/ORDA: 9-18-96

9609-161 (Closed) Gene Therapy/Phase I/Cancer/Small Cell Lung Cancer/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/Lipofectin(Gibco BRL)/B7-1(CD80) cDNA/Subcutaneous Injection

Antonia, Scott J.; H. Lee Moffitt Cancer Center, Tampa, Florida; *Treatment of Small Cell Lung Cancer Patients In Partial Remission Or At Relapse With B7-1 Gene-Modified Autologous Tumor Cells As A Vaccine With Systemic Interferon Gamma.*

Sole FDA Review Recommended by NIH/ORDA: 10-10-96
Closed: 1-23-98. Protocol Never Initiated

9610-162 (Open) Gene Therapy/Phase I/Cancer/Solid Tumors/Oncogene Regulation/HER-2/neu/ In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intratumoral Injection

LaFollette, Suzanne; Rush/Presbyterian/St. Luke's Medical Center, Chicago, Illinois; Murray, James L.; M.D. Anderson Cancer Center, Houston, Texas; Yoo, George; Wayne State University, Detroit, Michigan; *A Phase I Multicenter Study of Intratumoral E1A Gene Therapy for Patients with Unresectable or Metastatic Solid Tumors that Overexpress HER-2/neu.* Sponsor: Targeted Genetics Corporation

Sole FDA Review Recommended by NIH/ORDA: 10-29-96

9610-163 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/MART-1 Melanoma Antigen/Intramuscular Injection

Rosenberg, Steven A.; NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding The MART-1 Melanoma Antigen.*

Sole FDA Review Recommended by NIH/ORDA: 5-23-96

9610-164 (Closed) Gene Therapy/Phase I/Cancer/Liver(Hepatic)Metastases/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Sung, Max W.; and Woo, Savio L.C.; Mount Sinai Medical Center, New York, New York; *Phase I Trial of Adenoviral Vector Delivery of the Herpes Simplex Thymidine Kinase Gene by Intratumoral Injection Followed by Intravenous Ganciclovir in Patients with Hepatic Metastases.*

Sole FDA Review Recommended by NIH/ORDA: 11-12-96

9611-165 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/gp100 Melanoma Antigen/Intramuscular Injection

Rosenberg, Steven A.; NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding the GP100 Melanoma Antigen.*

NIH/ORDA Receipt Date: 11-13-96 . Sole FDA Review Recommended: 1-17-96

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9611-166 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Vaccinia Virus/MART-1 Melanoma Antigen/Intramuscular Injection

Rosenberg, Steven A.; NIH, Bethesda, Maryland; *Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Vaccinia Virus Encoding the MART-1 Melanoma Antigen.*

NIH/ORDA Receipt Date: 11-13-96. Sole FDA Review Recommended: 1-17-96

9611-167 (Closed) Gene Therapy/Phase II/Cancer/Glioblastoma/Pro-Drug/In Vivo/Autologous Tumor Cells/PA317/Retrovirus/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Direct Injection

Maria, Bernard, *et al.* (All #9608-157 sites are eligible to participate in this study.) *Prospective, Open-Label, Multicenter, Extension Trial for the Treatment of Recurrent Glioblastoma Multiforme with Surgery and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir for Patients with Disease Progression Following Standard Treatment on Protocol GTI-0115.* Sponsor: Genetic Therapy, Inc./Novartis
This protocol is an extension of #9608-157.

NIH/ORDA Receipt Date: 11-13-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97

9611-168 (Closed) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Hersh, Evan M.; Arizona Cancer Center, Tucson, Arizona; Klasa, Richard; British Columbia Cancer Agency, Vancouver, B.C., Canada; Gonzales, Rene; University of Colorado Cancer Center, Denver, Colorado; Silver, Gary; Northern California Melanoma Clinic, San Francisco, California; Thompson, John A.; U. of Washington Medical Center, Seattle, Washington; *Phase II Study of Immunotherapy of Metastatic Melanoma by Direct Gene Transfer.* Sponsor: Vical, Incorporated

NIH/ORDA Receipt Date: 11-26-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97

9611-169 (Closed) Gene Therapy/Phase I/II/Cancer/Solid Tumors/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL 1102/Cytokine/Interleukin-2 cDNA/Direct Intratumoral Injection

Hersh, Evan, M.; Arizona Cancer Center, Tucson, Arizona; Rinehart, John; Scott and White Clinic, Temple, Texas; Rubin, Joseph; Mayo Clinic, Rochester, Minnesota; Sondak, Vernon K.; University of Michigan Medical Center, Ann Arbor, Michigan; Gonzales, Rene; University of Colorado Cancer Center, Denver, Colorado; Sobol, Robert E.; Sharp HealthCare, San Diego, California; and Forscher, Charles A.; Cedars-Sinai Comprehensive Cancer Center, Los Angeles, California; *Phase I/II Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Cancer by Direct Gene Transfer.* Sponsor: Vical, Incorporated

NIH/ORDA Receipt Date: 11-26-96. Sole FDA Review Recommended by NIH/ORDA: 1-17-97

9612-170 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Lung and Nasal Epithelial Cells/Cationic Liposome Complex/DOPE/CFTR cDNA/Aerosol Administration

Sorscher, Eric; University of Alabama, Birmingham, Medical Center; *Safety and Efficiency of Gene Transfer of Aerosol Administration of a Single Dose of a Cationic Lipid/DNA Formulation to the Lungs and Nose of Patients with Cystic Fibrosis.* Sponsor: Genzyme Corporation

NIH/ORDA Receipt Date: 12-17-96. Sole FDA Review Recommended by NIH/ORDA: 1-6-97

9701-171 (Open) Non-Therapeutic/In Vivo/Intradermal Cells/Adenovirus/Serotype 5/E. coli Cytosine Deaminase/Intradermal Injection

Harvey, Ben-Gary; and Crystal, Ronald G.; Rockefeller University Hospital, New York, New York; *Immune Response to Intradermal Administration of an Adenovirus Type 5 Gene Transfer Vector ($Ad_{GV}CD.10$) in Normal Individuals.*

NIH/ORDA Receipt Date: 1-9-97. *RAC Recommends Approval: 3-6-97/NIH Approval: 4-21-97

9701-172 (Closed) Gene Therapy/Phase I/Cancer/Germ Cell Tumors (Testicular Cancer)/Chemoprotection/In Vitro/G-CSF Mobilized Autologous CD34+ Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Bone Marrow Transplant

Cornetta, Kenneth; and Abonour, Rafat; Indiana University Department of Medicine, Indianapolis, Indiana; *High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study.*

NIH/ORDA Receipt Date: 1-9-97. Sole FDA Review Recommended by NIH/ORDA: 2-26-97

Closed to patient accrual: 3-15-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9701-173 (Closed) Gene Therapy/Phase I/Cancer/Brain Tumors/Chemoprotection/In Vitro/Peripheral Blood CD34+ Cells/Retrovirus/O^6-Methylguanine DNA Methyltransferase cDNA/Intravenous Infusion

Croop, James; Indiana University School of Medicine, Indianapolis, Indiana; and Kieran, Mark, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine(PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^6-Methylguanine DNA Methyltransferase.*

NIH/ORDA Receipt Date: 1-13-97. Sole FDA Review Recommended by NIH/ORDA: 2-4-97

Notification that trial is closed to new research participant enrollment: 2-20-01

9701-174 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Interleukin-2 cDNA/Neomycin Phosphotransferase cDNA/Immunoisolation Device/Subcutaneous Implantation

Das Gupta, Tapas K.; University of Illinois at Chicago, Chicago, Illinois; *A Pilot Study Using Interleukin-2 Transfected Irradiated Allogeneic Melanoma Cells Encapsulated in an Immunoisolation Device In Patients with Metastatic Malignant Melanoma.*

NIH/ORDA Receipt Date: 1-13-97. Sole FDA Review Recommended by NIH/ORDA: 2-21-97

9701-175 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral/Stereotactic Injection

Lieberman, Frank; Germano, Isabelle; and Woo, Savio; Mount Sinai Medical Center, New York, New York; *Gene Therapy for Recurrent Glioblastoma Multiforme: Phase I Trial of Intraparenchymal Adenoviral Vector Delivery of the HSV-TK Gene and Intravenous Administration of Ganciclovir.*

NIH/ORDA Receipt Date: 1-22-97. Sole FDA Review Recommended by NIH/ORDA: 2-12-97

9702-176 (Open) Gene Therapy/Phase I/II/Cancer/Prostate Adenocarcinoma/Immunotherapy/In Vivo/Vaccination/Vaccinia Virus/Prostate Specific Antigen/Intradermal Injection

Sanda, Martin G.; University of Michigan Urology Clinics, Ann Arbor, Michigan; *A Phase I/II Clinical Trial Evaluating the Safety and Biological Activity of Recombinant Vaccinia-PSA Vaccine in Patients with Serological Recurrence of Prostate Cancer Following Radical Prostatectomy.*

NIH/ORDA Receipt Date: 2-19-97. Sole FDA Review Recommended by NIH/ORDA: 5-13-97

9702-177 (Open) Gene Marking/Cancer/Chronic Myelogenous Leukemia/In Vitro/Autologous Peripheral Blood Cells Mobilized by Cyclophosphamide and G-CSF/Retrovirus/Neomycin Phosphotransferase cDNA/Autologous Bone Marrow Transplant

Verfaille, Catherine; McIvor, Scott; McCullough, Jeff; and McGlave, Philip; University of Minnesota, Minneapolis, Minnesota; *Autologous Marrow Transplantation for Chronic Myelogenous Leukemia Using Retrovirally Marked Peripheral Blood Progenitor Cells Obtained after In Vivo Cyclophosphamide/G-CSF Priming.*

NIH/ORDA Receipt Date: 2-21-97. Sole FDA Review Recommended by NIH/ORDA: 3-14-97

9703-178 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD34+ Autologous Cord Blood Cells/Retrovirus/Transdominant Trev/Intravenous

Belmont, John W.; Texas Children's Hospital, Houston, Texas; *Phase I Clinical Trial of TREV Gene Therapy for Pediatric AIDS.*

NIH/ORDA Receipt Date: 3-10-97. Sole FDA Review Recommended by NIH/ORDA: 3-31-97

9703-179 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Carcinoembryonic Antigen/Intravenous

Lyerly, Kim H.; Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Active Immunotherapy With Carcinoembryonic Antigen RNA-Pulsed Autologous Human Cultured Dendritic Cells In Patients with Metastatic Malignancies Expressing Carcinoembryonic Antigen.*

NIH/ORDA Receipt Date: 3-14-97. Publicly Reviewed at the June 1997 RAC meeting.

Sole FDA Review Recommended by NIH/ORDA: 6-24-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9703-180 (Open) Gene Therapy/Phase I/Other/Cubital Tunnel Syndrome/In Vivo/Autologous Muscle Cells/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Human Insulin-Like Growth Factor-1(hIGF-1)/Intramuscular Injection

Netscher, David; Hand Clinic at the Veteran's Affairs (VA) Medical Center, Houston, Texas; *Phase I Single Dose-Ranging Study Of Formulated hIGF-1 Plasmid In Subjects With Cubital Tunnel Syndrome.* Sponsor: Gene Medicine, Inc.

NIH/ORDA Receipt Date: 3-17-97. Sole FDA Review Recommended: 4-7-97

9703-181 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD8 + and CD4+ T Lymphocytes/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous/Concurrent Interleukin-2 Therapy

Connick, Elizabeth; University of Colorado Health Sciences Center, Denver, Colorado; Deeks, Steven G.; University of California, San Francisco General Hospital, San Francisco, California; Scadden, David; Massachusetts General Hospital (East), Charlestown, Massachusetts; Mitsuyasu, Ronald; University of California, Los Angeles Medical Center, Los Angeles, California; *A Phase II Study of the Activity and Safety of Autologous CD4-Zeta Gene-Modified T Cells With or Without Exogenous Interleukin-2 in HIV Infected Patients.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 3-19-97. Sole FDA Review Recommended: 4-18-97

Notification from sponsor that trial is closed: 4-09-01

9703-182 (Open) Gene Therapy/Phase II/Monogenic Inherited Disorder/Cystic Fibrosis/Sinusitis/Correction/In Vivo/Maxillary Sinus Epithelial Cells/ Adeno-associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Maxillary Sinus Administration

Gardner, Phyllis; Stanford University's General Clinical Research Center (GCRC), Palo Alto, California; *A Phase I/II Study of tgAAVCF for the Treatment of Chronic Sinusitis With Cystic Fibrosis.* Sponsor: Targeted Genetics Corporation

NIH/ORDA Receipt Date: 3-13-97. Sole FDA Review Recommended: 4-1-97

9703-183 (Closed) Gene Marking/Cancer/EBV-Positive Hodgkin Disease/In Vitro/EBV-Specific Hodgkin Disease/In Vitro/EBV-Specific Cytotoxic Lymphocytes/Retrovirus/Neomycin Phosphotransferase/Bone Marrow Transplant

Straus, Stephan E.; National Institutes of Health, Bethesda, Maryland; *Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T-Lymphocytes To Patients With Relapsed EBV-Positive Hodgkin Disease.*
Compassionate Case

NIH/ORDA Receipt Date: 3-19-97. Sole FDA Review Recommended by NIH/ORDA: 3-25-97

Patient never treated (closed as of 11-18-97)

9703-184 (Closed) Gene Therapy/Phase I/Cancer/Prostate Cancer/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1102/Cytokine/Interleukin-2 cDNA/Intratumoral Injection

Belldegrun, Arie; University of California, Los Angeles, School of Medicine, Los Angeles, California; *A Phase I Study Evaluating the Safety and Efficacy of Interleukin-2 Gene Therapy Delivered by Lipid Mediated Gene Transfer (Leuvectin) in Prostate Cancer Patients.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 3-24-97. Sole FDA Review Recommended by NIH/ORDA: 5-21-97

9704-185 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Melanoma Cell/Canarypox Virus/Cytokine/Interleukin-12 cDNA/Intratumoral Injection

Conry, Robert M.; University of Alabama at Birmingham, Birmingham, Alabama; *Phase Ib Trial of Intratumoral Injection of a Recombinant Canarypox Virus Encoding the Human Interleukin-12 Gene (ALVAC-hIL-12) in Patients with Surgically Incurable Melanoma* Sponsor: NCI- Cancer Therapy Evaluation Program

NIH/ORDA Receipt Date: 4-1-97. Sole FDA Review Recommended by NIH/ORDA: 7-2-97

9704-186 (Closed) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Nasal Epithelial Cells/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Cationic Liposome Complex/EDMPC/Intranasal Administration

Noone, Peadar G.; Knowles, Michael R.; University of North Carolina at Chapel Hill, North Carolina; *A Double-Blind, Placebo Controlled, Dose Ranging Study to Evaluate the Safety and Biological Efficacy of the Lipid-DNA Complex GR213487B in the Nasal Epithelium of Adult Patients with Cystic Fibrosis.* Sponsor: Glaxo Wellcome Inc.

NIH/ORDA Receipt Date: 4-23-97. Sole FDA Review Recommended by NIH/ORDA: 5-13-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9705-187 (Closed) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug/In Vivo/AutologousTumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Hall, Simon J.; Woo, Savio L.C.; Mount Sinai School of Medicine, New York, New York; *Phase I Trial of Adenoviral-Mediated Herpes Simplex Thymidine Kinase Gene Transduction in Conjunction with Ganciclovir Therapy as Neo-adjuvant Treatment for Patients with Clinically Localized (Stage T1c and T2b&c) Prostate Cancer Prior to Radical Prostatectomy.*

NIH/ORDA Receipt Date: 5-7-97. Sole FDA Review Recommended by NIH/ORDA: 5-28-97
Closed to accrual: 11-12-01

9705-188 (Open) Gene Therapy/Phase I/Cancer/Chronic Myelogenous Leukemia/Chemoprotection/Tyr-22 Murine Dihydrofolate Reductase Gene/Antisense/Anti-b3a2BCR/ABL Gene/In Vitro/Autologous Peripheral Blood CD34+ Cells Mobilized by Cyclophosphamide and G-CSF/Retrovirus/Autologous Bone Marrow Transplant

Verfaillie, Catherine; McIvor, Scott; McCullough, Jeff; McGlave, Philip; University of Minnesota, Minneapolis, Minnesota; *Autologous Transplantation for Chronic Myelogenous Leukemia with Stem Cells Transduced with a Methotrexate Resistant DHFR and Anti-BCR/ABL Containing Vector and Post Transplant Methotrexate Administration.*

NIH/ORDA Receipt Date: 5-16-97. Sole FDA Review Recommended by NIH/ORDA: 6-6-97

9705-189 (Closed) Gene Therapy/Phase I/Cancer/Hepatocellular Carcinoma/Tumor Suppressor Gene/In Vivo/Autologous nTumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Belani, Chandra P.; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; *Phase I Study of Percutaneous Injections of Adenovirus p53 Construct (Adeno-p53) for Hepatocellular Carcinoma.*

NIH/ORDA Receipt Date: 5-27-97. Sole FDA Review Recommended by NIH/ORDA: 9-19-97

Closed: 3-7-00

9705-190 (Open) Gene Therapy/Phase I/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DOTMA-Cholesterol/Cytokine/Interleukin-2 cDNA/Intratumoral Injection

O'Malley, Bert W.; Johns Hopkins Medical Institutions, Baltimore, Maryland; *A Double-Blind, Placebo-Controlled, Single Rising-Dose Study of the Safety and Tolerability of Formulated hIL-2 Plasmid in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Gene Medicine, Inc.

NIH/ORDA Receipt Date: 5-27-97. Sole FDA Review Recommended by NIH/ORDA: 6-16-97

9706-191 (Closed) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Direct Intratumoral Injection

Gluckman, Jack L..; Gleich, Lyon L., University of Cincinnati Medical Center, Cincinnati, Ohio; Swinehart, James M.; Colorado Medical Research Center, Denver, Colorado; Hanna, Ehab; University of Arkansas for Medical Sciences/Arkansas Cancer Research Center (UAMS), Little Rock, Arkansas; Castro, Dan J.; University of California, Los Angeles, Los Angeles, California; Gapany, Markus; Veterans Affairs Medical Center, Minneapolis, Minnesota; Carroll, William R.; University of Alabama at Birmingham, Birmingham, Alabama; Coltrera, Marc D.; University of Washington Medical Center, Seattle, Washington; Wolf, Gregory T.; University of Michigan Medical Center, Ann Arbor, Michigan; and Okuno, Scott; Mayo Clinic, Rochester, Minnesota; *Phase II Study of Immunotherapy by Direct Gene Transfer with Allovectin-7 for the Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 6-6-97. Sole FDA Review Recommended by NIH/ORDA: 7-7-97

9706-192 (Open) Gene Therapy/Phase I/Cancer/Prostate/Tumor suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Belldegrun, Arie; and Figlin, Robert.; UCLA School of Medicine, Los Angeles, California; *A Phase I Study in Patients with Locally Advanced or Recurrent Adenocarcinoma of the Prostate Using SCH58500 (rAd/p53) Administered by Intratumoral Injection.* Sponsor: Schering-Plough Corporation

NIH/ORDA Receipt Date: 6-9-97. Sole FDA Review Recommended by NIH/ORDA: 9-17-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9706-193 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/CEA-Expressing Malignancies/In Vivo/Autologous Muscle Cells/Canarypox Virus/Vaccinia Virus/Carcinoembryonic Antigen cDNA/Intramuscular and Percutaneous Injection

Marshall, John L.; Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C.; *A Pilot Study of Sequential Vaccinations with ALVAC-CEA and Vaccinia-CEA with the Addition of IL-2 and GM-CSF in Patients with CEA Expressing Tumors.* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-18-97. Sole FDA Review Recommended by NIH/ORDA: 9-18-97

9706-194 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Immunotherapy/In Vivo/Autologous Muscle Cells/Retrovirus/HIV-1 IIIB Envelope Protein/Intramuscular Injection

Aboulafia, David; Virginia Mason Clinic, Seattle, Washington; Campbell, Thomas; University of Colorado Health Sciences Center, Denver, Colorado; Kumar, Princy; Georgetown University Medical Center, Washington, D.C.; Murphy, Robert; Northwestern University Medical School, Chicago, Illinois; Skolnik, Paul; New England Medical Center, Boston, Massachusetts; and Wheat, Joseph; Indiana University Hospital, Indianapolis, Indiana; *A Phase II, Randomized, Double Blind Placebo Controlled Study of Combination Drug Anti-Retroviral Therapy to Include a Reverse Transcriptase Inhibitor and a Protease Inhibitor Plus HIV-IT(V) or Placebo in HIV Patients with CD4+ Counts $\geq$ 100, and HIV RNA $\geq$ 1K, and $\leq$ 10K.* Sponsor: Chiron Corporation

NIH/ORDA Receipt Date: 6-23-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97
5-10-00: IND no longer active

9706-195 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/CEA-Expressing Malignancies/In Vivo/Vaccinia Virus/Carcinoembryonic Antigen cDNA/Intradermal and Subcutaneous Injections

Conry, Robert M.; The University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Trial of a Recombinant Vaccinia-CEA (180 Kd) Vaccine Delivered by Intradermal Needle Injection Versus Subcutaneous Jet Injection in Patients with Metastatic CEA-Expressing Adenocarcinoma.* Sponsor: Drug Regulatory Affairs Branch, Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment, Diagnosis and Centers, NCI, NIH

NIH/ORDA Receipt Date: 6-26-97. Sole FDA Review Recommended by NIH/ORDA: 9-5-97

9706-196 (Open) Gene Therapy/Phase I/Monogenic Disease/Chronic Granulomatous Disease/In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/gp91phox/Intravenous Infusion

Croop, James; Indiana University School of Medicine, Indianapolis, Indiana; *Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study.*

NIH/ORDA Receipt Date: 6-30-97. Sole FDA Review Recommended by NIH/ORDA: 7-21-97

9706-197 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Melanoma Cell/Canarypox Virus/B7(CD80)/Interleukin-12/Cytokine/Intratumoral Injection

Conry, Robert M.; University of Alabama at Birmingham, Birmingham, Alabama; *Phase Ib Trial of Intratumoral Injection of a Recombinant Canarypox Virus Encoding Human B7.1 (ALVAC-hB7.1) or a Combination of ALVAC-hB7.1 and a Recombinant Canarypox Virus Encoding Human Interleukin-12 (ALVAC-hIL-12) in Patients with Surgically Incurable Melanoma.* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-30-97. Sole FDA Review Recommended by NIH/ORDA: 9-5-97

9707-198 (Closed) Gene Therapy/Phase I/II/Cancer/Colorectal Carcinoma Expressing TAG-72/In Vitro/Autologous CD8+ and CD4+ T Lymphocytes/Retrovirus/CC49-Zeta T Cell Receptor/Intravenous Infusion

Venook, Alan and Warren, Robert S.; University of California, San Francisco, California and Fisher, George; Stanford University, Palo Alto, California; *A Phase I/II Study of Autologous CC49-Zeta Gene-Modified T Cells and α-Interferon in Patients with Advanced Colorectal Carcinomas Expressing the Tumor-Associated Antigen, TAG-72.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 7-7-97. Sole FDA Review Recommended by NIH/ORDA: 8-28-97

Notification from sponsor that trial is closed: 4-09-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9707-199 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Breast/Head and Neck Cancer/Cutaneous T-Cell Lymphoma/Immunotherapy/In Vitro/Autologous Fibroblasts/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-12/Intratumoral Injection

Park, Chan H.; Samsung Medical Center, Seoul, Korea; Kim, Sunyoung; Seoul National University, Seoul, Korea; Lotze, Michael; Tahara, Hideaki; and Robbins, Paul; University of Pittsburgh, Pittsburgh, Pennsylvania; *IL-12 Gene Therapy Using Direct Injection of Tumors with Genetically Engineered Autologous Fibroblasts.*

NIH/ORDA Receipt Date: 7-22-97. Sole FDA Review Recommended by NIH/ORDA: 10-30-97

9707-200 (Open) Gene Therapy/Phase I/II/Cancer/Non-Hodgkin's B-Cell Lymphoma/Mantle Cell Lymphoma/Immunotherapy/In Vivo/Naked Plasmid DNA/Tumor Idiotype/Intramuscular Injection

Levy, Ronald; Stanford University School of Medicine, Stanford, California; *A Phase I/II Study of Vaccine Therapy for B-Cell Lymphoma Utilizing Plasmid DNA Coding for Tumor Idiotype.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 7-24-97. Sole FDA Review Recommended by NIH/ORDA: 8-13-97

9707-201 (Open) Gene Therapy/Phase I/ Cancer/Ovarian/Immunotherapy/In Vitro/Autologous Tumor Cells/Canarypox Virus/B7.1 (CD80)/Intraperitoneal Injection

Freedman, Ralph; The University of Texas, M.D. Anderson Cancer Center, Houston, Texas; *Intraperitoneal (IP) Autologous Therapeutic Tumor Vaccine (AUT-OV-ALVAC-hB7.1) plus IP rIFN-γ for Patients with Ovarian Cancer. A Pilot Study.* Sponsor: NCI Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-202 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Melanoma/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Dranoff, Glenn and Soiffer, Robert; Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Lethally Irradiated Melanoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.*

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-203 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Non-Small Cell Lung Carcinoma (NSCLC)/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Dranoff, Glenn and Salgia, Ravi; Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Vaccination with Autologous, Lethally Irradiated Non-Small Cell Lung Carcinoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor.*

NIH/ORDA Receipt Date: 7-28-97. Sole FDA Review Recommended by NIH/ORDA: 8-15-97

9707-204 (Closed) Gene Therapy/Phase I/Monogenic Disease/Leukocyte Adherence Deficiency (LAD)/In Vitro/G-CSF Mobilized CD34+ Autologous Peripheral Blood Cells/Retrovirus/CD18/Intravenous Infusion

Hickstein, Dennis and Bauer, Thomas R. National Institutes of Health, Bethesda, Maryland; *Retrovirus-Mediated Transfer of the cDNA for Human CD18 into Peripheral Blood Repopulating Cells of Patients with Leukocyte Adherence Deficiency.*

NIH/ORDA Receipt Date: 7-31-97. Sole FDA Review Recommended by NIH/ORDA: 9-17-97
Closed: 9-17-00

9708-205 (Closed) Gene Therapy/Phase I/II/Cancer/Prostate/Immunotherapy/ In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Simons, Jonathan W.; Johns Hopkins Oncology Center, Baltimore, Maryland; *Phase I/II Study of Allogeneic Human GM-CSF Gene Transduced Irradiated Prostate Cancer Cell Vaccines in Patients with Prostate Cancer.*

NIH/ORDA Receipt Date: 8-19-97. Sole FDA Review Recommended by NIH/ORDA: 9-9-97

Closed: 7-23-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9708-206 (Closed) Gene Therapy/Phase I/II/Cancer/Chronic Myelogenous Leukemia/Adoptive Immunotherapy/In Vitro/Donor CD8+ and CD4+ Lymphocytes/Retrovirus/Hygromycin Phosphotransferase-Herpes Simplex Thymidine Kinase Fusion Gene/Intravenous Infusion

Flowers, Mary E. D. and Riddell, Stanley; Fred Hutchinson Cancer Research Center, Seattle, Washington; *Infusion of Polyclonal HyTK (hygromycin phosphotransferase and HSV thymidine kinase gene)-transduced Donor T Cells for Adoptive Immunotherapy in Patients with Relapsed CML after Allogeneic Stem Cell Transplant: Phase I-II Clinical Trial.*

NIH/ORDA Receipt Date: 8-19-97. Sole FDA Review Recommended by NIH/ORDA: 9-26-97
Closed to new accrual: 4-24-00.

9708-207 (Closed) Gene Therapy/Phase I/Cancer/Colorectal/Immunotherapy/In Vivo/Autologous Tumor Cells/Canarypox Virus/Carcinoembryonic Antigen/B7.1 (CD80)/Intradermal Scarification

Kaufman, Howard L.; Albert Einstein Cancer Center, Bronx, New York; *Phase I Clinical Trial of a Recombinant ALVAC-CEA-B7 Vaccine in the Treatment of Advanced Colorectal Carcinoma.* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 8-21-97. Sole FDA Review Recommended by NIH/ORDA: 11-25-97
Closed: 2-99.

9708-208 (Open) Gene Therapy/Phase I/Cancer/Mesothelioma/Pro-Drug/In Vivo/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Herpes Simplex Virus Thymidine Kinase/Ganciclovir/Intrapleural Administration

Schwarzenberger, Paul; Louisiana State University Medical Center, New Orleans, Louisiana; *The Treatment of Malignant Pleural Mesothelioma with a Gene-Modified Cancer Vaccine: A Phase I Study.*

NIH/ORDA Receipt Date: 8-25-97. Sole FDA Review Recommended by NIH/ORDA: 9-16-97

9708-209 (Closed) Non-Therapeutic/In Vivo/Bronchial Epithelial Cells/Adenovirus/Serotype 5/*E. coli* Cytosine Deaminase/Intrabronchial Administration

Harvey, Ben-Gary and Crystal, Ronald G.; Rockefeller University Hospital, New York, New York; *Systemic and Respiratory Immune Response to Administration of an Adenovirus Type 5 Gene Transfer Vector ($Ad_{GV}CD.10$).*

NIH/ORDA Receipt Date: 8-26-97. Publicly Reviewed at the December 16, 1997 RAC meeting
Closed: 09-19-00

9709-210 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/β2-Macroglobulin cDNA/Direct Intratumoral Injection

Gonzales, Rene; University of Colorado Cancer Center, Denver, Colorado; Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; Deisseroth, Albert, Yale University, New Haven, Connecticut; Paciucci, Paolo A., Mt. Sinai Medical Center, New York, New York; Hutchins, Laura F., University of Arkansas for Medical Sciences, Little Rock, Arkansas; Galanis, Evanthia, Mayo Clinic, Rochester, Minnesota; Schaefer, Paul L., Toledo Clinic, Toledo, Ohio; Amatruda, Thomas, Virginia Piper Cancer Institute Abbott Northwestern Hospital, Minneapolis, Minnesota; Kuzel, Timothy, Northwestern Medical Faculty Foundation Northwestern Memorial Hospital, Chicago, Illinois; Blum, Ronald H., Beth Israel Medical Center, Phillips Ambulatory Care Center, New York, New York; Whitman, Eric D., The Melanoma Center of St. Louis, Saint Louis, Missouri; Cobb, Patrick, Billings Interhospital Oncology Project, Billings, Montana; Amin, Bipinkumar, Mid Dakota Clinic, Bismarck, North Dakota; Chowhan, Naveed, Cancer Care Center Incorporated, New Albany, Indiana; Lutzky, Jose, Mount Sinai Medical Center, Miami, Florida; Amatruda, Thomas, North Memorial Healthcare, Hubert H. Humphrey Cancer Center, Robbinsdale, Minnesota ;Patel, Ravi, Comprehensive Blood and Cancer Center, Bakersfield, California; Dobbs, Tracy W., Baptist Hospital of East Tennessee, Knoxville, Tennessee; Ahmed, Fakhiuddin, HemOnCare, P.C., Brooklyn, New York; Thant, Myo, Maryland Hematology/Oncology Associates, Baltimore, Maryland; Stark, James J., Maryview Medical Center, Portsmouth, Virginia; Arena, Francis, Arena Oncology Associates, Great Neck, New York; Soori, Gamini, Alegent Health, Bergan Mercy Medical Center, Omaha, Nebraska; Samlowski, Wolfram, University of Utah Health Sciences Center; Huntsman Cancer Institute, Salt Lake City, Utah; Polikoff, Jonathan A., Kaiser Permanente Medical Group, San Diego, California; Hawkins, Michael, Washington Hospital Center, Washington Cancer Institute, Washington, D.C.; Richart, John, Saint Louis University Health Sciences Center, St. Louis, Missouri; Patel, Taral, Columbus, Community Clinical Oncology Program, Columbus, Ohio; Levine, Edward, Wake Forest University School of Medicine, Winston Salem, North Carolina; Richards, Jon, Lutheran General Hospital, Park Ridge, Illinois; and Thompson, John A., University of Washington Medical Center, Seattle, Washington; *Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 9-8-97. Sole FDA Review Recommended by NIH/ORDA: 9-26-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9708-211 (Open) Gene Therapy/Phase I/Monogenetic Disease/Canavan Disease/In Vivo/Autologous Brain Cells/Plasmid DNA/Adeno-associated Virus/Poly-L-Lysine/Cationic Liposome Complex/DC-Chol/DOPE/Aspartoacylase cDNA/Intracranial (Ommaya Reservoir) Administration

Seashore, Margretta R.; Yale University, New Haven, Connecticut; *Gene Therapy of Canavan Disease: Retreatment of Previously Treated Children.*

NIH/ORDA Receipt Date: 8-28-97. Publicly Reviewed at the December 16, 1997 RAC meeting

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9709-212 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE Vical VCL-1005/HLA-B7/Beta-2 Microglobulin cDNA/Vical-1102/Interleukin-2 cDNA/Intratumoral Injection

Gonzalez, Rene; University of Colorado Health Sciences Center, Denver, Colorado; Hersh, Evan M.; Arizona Cancer Center, Tucson, Arizona; Rubin, Joseph; Mayo Clinic, Rochester, Minnesota; and Thompson, John A.; University of Washington Medical Center, Seattle, Washington; *Phase I Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) with IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Melanoma.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 9-18-97. Sole FDA Review Recommended by NIH/ORDA: 10-8-97

9709-213 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD8+ T Cells/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous

Deeks, Steven G.; University of California, San Francisco General Hospital, San Francisco, California; *A Phase II Study of Autologous CD4-Zeta Gene-Modified T Cells in HIV-Infected Patients with Undetectable Plasma Viremia on Combination Antiretroviral Drug Therapy.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 9-22-97. Sole FDA Review Recommended by NIH/ORDA: 10-10-97

Study closed to new accrual, follow-up is continuing: 7-13-01

9709-214 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53

Breau, Randall L.; University of Arkansas for Medical Sciences, Little Rock, Arkansas; Clayman, Gary L.; The University of Texas MD Anderson Cancer Center, Houston, Texas; Yoo, George H.; Wayne State University/Barbara Ann Karmanos Cancer Institute, Detroit, Michigan; Medina, Jesus E.; University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; Murphy, Barbara S.; Vanderbilt University Medical Center, Nashville, Tennessee; Goodwin, W. Jarrard; University of Miami Hospitals and Clinics, Miami, Florida; Weber, Jeffery S.; University of Southern California, Los Angeles, California; Schuller, David E.; Ohio State University Medical Center, Columbus, Ohio; Bukowski, Ronald M.; The Cleveland Clinic Foundation, Cleveland, Ohio; Hamm, John; University of Louisville Health Sciences Center, Louisville, Kentucky; Agarwala, Sanjiv; University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; Hochster, Howard S.; New York University Medical Center, New York, New York; Dietz, Andreas; University of Heidelberg, Heidelberg, Germany; Eβer, Dirk; Ear, Nose and Throat Clinic, Erfurt, Germany; and Flood, William A.; Milton S. Hershey Medical Center, Hershey, Pennsylvania; *A Phase II Multi-Center, Open Label, Randomized Study to Evaluate Effectiveness and Safety of Two Treatment Regimens of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Aventis (formerly Gencell)

NIH/ORDA Receipt Date: 9-22-97. Sole FDA Review Recommended by NIH/ORDA: 10-21-97

9709-215 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vivo/Autologous Tumor Cells/Canarypox Virus/Carcinoembryonic Antigen/B7.1 (CD80)/Intramuscular and Intradermal Injections

von Mehren, Margaret; Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I/Pilot Study of ALVAC-CEA-B7.1 Immunization in Patients with Advanced Adenocarcinoma Expressing CEA.* Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 9-24-97. Sole FDA Review Recommended by NIH/ORDA: 10-28-97

9709-216 (Open) Gene Therapy/Phase I/Cancer/Breast/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Cutaneous or Subcutaneous

von Mehren, Margaret; Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I/Pilot Study of p53 Intralesional Gene Therapy with Chemotherapy in Breast Cancer .* Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 9-24-97. Sole FDA Review Recommended by NIH/ORDA: 10-28-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9710-217 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Logothetis, Christopher J.; University of Texas MD Anderson Cancer Center, Houston, Texas; *A Tolerance and Efficacy Study of Intraprostatic INGN 201 Followed by Pathological Staging and Possible Radical Prostatectomy in Patients with Locally Advanced Prostate Cancer.* Sponsor: Introgen Therapeutics, Inc.

NIH/ORDA Receipt Date: 10-3-97. Sole FDA Review Recommended by NIH/ORDA: 11-6-97

9710-218 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Hammerhead Ribozyme/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Tat and Rev Hammerhead Ribozyme/Intravenous

Krishnan, Amrita and Zaia, John, A.; City of Hope Medical Center, Duarte, California; *High Dose Chemotherapy and Autologous Peripheral Stem Cell Transplantation for HIV Lymphomas: A Phase IIa Study of Comparative Marking Using a Ribozyme Gene and a Neutral Gene.* Sponsor: Ribozyme Pharmaceuticals, Inc.

NIH/ORDA Receipt Date: 10-6-97. Sole FDA Review Recommended by NIH/ORDA: 10-27-97

9710-219 (Open) Gene Therapy/Phase I/Cancer/Bladder/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intravesical Administration

Pagliaro, Lance C.; The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I Trial of Intravesical Ad-p53 Treatment in Locally Advanced and Metastatic Bladder Cancer.*

NIH/ORDA Receipt Date: 10-21-97. Sole FDA Review Recommended by NIH/ORDA: 11-10-97

9710-220 (Open) Gene Therapy/Phase II/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Bronchoscopy or Percutaneous Intratumoral Injection

Dobbs, Tracy W.; East Tennessee Oncology/Hematology, P.C., Knoxville, Tennessee; *A Phase II Gene Therapy Study in Patients with Non-Small Cell Lung Cancer Using SCH 58500 (rAd/p53) in Combination with Chemotherapy for Multiple Cycles.* Sponsor: Schering Plough Research Institute

NIH/ORDA Receipt Date: 10-31-97. Not Selected for RAC Public Review: 12-15-97

9711-221 (Open) Gene Therapy/Phase I/Other/ Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Administration

Crystal, Ronald G.; The New York Hospital-Cornell Medical Center, New York, New York; *Phase I Study of Direct Administration of a Replication-Deficient Adenovirus Vector ($Ad_{GV}VEGF121.10$) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Life Threatening Diffuse Coronary Artery Disease.* Sponsor: Parke-Davis Pharmaceutical Research.

NIH/ORDA Receipt Date: 11-4-97. Publicly Reviewed at the December 16, 1997 RAC meeting

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9711-222 (Open) Gene Therapy/Phase I/Monogenetic Disease/Canavan Disease/In Vivo/Autologous Brain Cells/Plasmid DNA/Adeno-Associated Virus/Protamine/Cationic Liposome Complex/DC-Cholesterol-DOPE/Aspartoacylase cDNA/Intracranial (Ommaya Reservoir)

Freese, Andrew; Thomas Jefferson University, Philadelphia, Pennsylvania; *Gene Therapy of Canavan Disease.*

NIH/ORDA Receipt Date: 11-12-97. Not Selected for RAC Public Review: 1-26-98

9712-223 (Open) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Allogeneic Neuroblastoma Cell Lines/Retrovirus/Cytokine/Interleukin-2 (IL-2)/Plasmid/Electroporation/Chemokine/Lymphotactin/Subcutaneous Injection

Hale, Gregory; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Chemokine and Cytokine Gene Modified Allogeneic Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using a Retroviral Vector.*

NIH/ORDA Receipt Date: 12-3-97. Not Selected for RAC Public Review: 12-29-97

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9712-224 (Open) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Autologous Tumor Cells (Non-Irradiated)/Type 5 Adenovirus/Cytokine/Interleukin-2 (IL-2)/Chemokine/Lymphotactin/Subcutaneous Injection

Hale, Gregory; St. Jude Children's Research Hospital, Memphis, Tennessee; *Phase I Study of Chemokine and Cytokine Gene Modified Autologous Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using an Adenoviral Vector.*

NIH/ORDA Receipt Date: 12-3-97. Not Selected for RAC Public Review: 12-29-97

9712-225 (Closed) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/In Vitro/Antisense TAR/Transdominant Rev/Intravenous

Isola, Luis M.; Mount Sinai Medical Center, New York, New York; *A Phase I Trial of Autologous and Allogeneic Bone Marrow Transplantation with Genetically Marked Cells for the Treatment of HIV Associated Lymphoid Malignancies.*

NIH/ORDA Receipt Date: 12-15-97. Not Selected for RAC Public Review: 1-7-98
IND withdrawn: 4-4-00

9712-226 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injections

Dreicer, Robert; University of Iowa College of Medicine, Iowa City, Iowa; Simon, George R.; University of Colorado Health Sciences Center, Denver, Colorado; Williamson, Stephen; University of Kansas Medical Center, Kansas City, Kansas; VanEcho, David A.; University of Maryland School of Medicine, Baltimore, Maryland; Rosen, Fred; University of Illinois at Chicago Hospitals & Clinics; Endicott, James N.; University of South Florida, Tampa, Florida; Bier-Laning, Carol M.; University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; Minn, Heikki; Turku University Central Hospital, Turku Finland; Guertin, Louis; CHUM - Pavilion Notre-Dame, Montreal, Quebec; Liu, Fei-Fei; Princess Margaret Hospital, Toronto, Ontario; Wadler, Scott; Montefiore Medical Center, Albert Einstein College of Medicine; Bronx, New York; Goss, Glenwood D.; Ottawa Regional Cancer Centre, Ottawa, Ontario; Saarilanti, Kauko; Helsinki University Central Hospital, Helsinki Finland; Mudad, Raja; Tulane University Medical Center, New Orleans, Louisiana; Spiro, Jeffrey; University of Connecticut Health Center, Farmington, Connecticut; Zielinski, Christoph, University of Vienna; Link, Brian, University of Iowa Hospital and Clinics, Iowa City, Iowa; and Truelson, John, University of Texas Southwestern Medical School, Dallas, Texas; *A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Aventis (formerly Gencell)

NIH/ORDA Receipt Date: 12-17-97. Not Selected for RAC Public Review: 1-9-98

9801-227 (Closed) Gene Therapy/Phase II/Cancer/Melanoma/Head and Neck Cancer/Immunotherapy/In Vitro/Autologous Fibroblasts/Lethally Irradiated/Retrovirus/Cytokine/Interleukin-12 cDNA/Neomycin Phosphotransferase cDNA/Intratumoral Injection

Lotze, Michael T.; University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; *IL-12 Gene Therapy Using Direct Injection of Tumors with Genetically Engineered Autologous Fibroblasts (A Phase II Study).*

NIH/ORDA Receipt Date: 1-2-98. Not Selected for RAC Public Review: 2-18-98
Protocol is terminated: 11-1-01

9801-228 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/In Vivo/ Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Acyclovir/Intraperitoneal Injection

Kieback, Dirk G.; Baylor College of Medicine, Houston, Texas; *Phase I Study of Concomitant Adenovirus-Mediated Transduction of Ovarian Cancer with HSV-tk Gene Followed by Intravenous Administration of Acyclovir and Chemotherapy with Topotecan in Patients after Optimal Debulking Surgery for Recurrent Ovarian Cancer.*

NIH/ORDA Receipt Date: 1-14-98. Not Selected for RAC Public Review: 2-5-98

9801-229 (Open) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Kadmon, Dov; Baylor College of Medicine, Houston, Texas; *Neoadjuvant Pre-radical Prostatectomy Gene Therapy (HSV-tk Gene Transduction Followed by Ganciclovir) in Patients with Poor Prognostic Indicators.*

NIH/ORDA Receipt Date: 1-16-98. Not Selected for RAC Public Review: 2-13-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9801-230 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/Antisense TAR/Antisense tat | rev/In Vitro/CD34+ Cells/Intravenous

Cowan, Morton J. and Conant, Marcus A.; University of California, San Francisco, San Francisco, California; *Evaluation of the Safety and Effects of Ex Vivo Modification and Re-infusion of CD34+ Cells by an Antisense Construct Against HIV-1 in a Retroviral Vector.* Sponsor: Enzo Therapeutics, Inc.

NIH/ORDA Receipt Date: 1-20-98. Not Selected for RAC Public Review: 3-26-98

9802-231 (Open) Gene Therapy/Phase I/II/Monogenic Disease/Chronic Granulomatous Disease/In Vitro/CD 34+ Autologous Peripheral Blood Cells/Retrovirus/p47phox/gp91phox/Intravenous

Malech, Harry L.; National Institutes of Health, Bethesda, Maryland; *Gene Therapy Approach for Chronic Granulomatous Disease.*

NIH/ORDA Receipt Date: 2-2-98. Not Selected for RAC Public Review: 2-20-98

9802-232 (Closed) Gene Therapy/Phase I/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Administration

Isner, Jeffrey M.; Tufts University School of Medicine, Boston, Massachusetts; *Gene Therapy for Myocardial Angiogenesis.*

NIH/ORDA Receipt Date: 2-3-98. Publicly Reviewed at the June 18, 1998 RAC meeting
Follow-up has been completed: 11-29-01

9802-233 (Closed) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral Injection

Dreicer, Robert; the University of Iowa Hospitals and Clinics, Iowa City, Iowa; Seigler, Hilliard; Duke University Medical Center, Durham, North Carolina; Rubin, Joseph; Mayo Clinic, Rochester, Minnesota; DeConti, Robert; H. Lee Moffitt Cancer Center, Tampa, Florida; Gonzalez, Rene; the University of Colorado Cancer Center, Denver Colorado; Macdonald, John S.; Saint Vincent's Hospital and Medical Center, New York, NY; Hutchins, Laura; University of Arkansas for Medical Sciences, Little Rock, Arkansas; Samlowski, Wolfram E.; the University of Utah Health Sciences Center, Salt Lake City, Utah; Bearden, James D.; Spartanburg Regional Medical Center, Spartanburg, South Carolina; Atkins, Michael B., Beth Israel Medical Center, Boston, Massachusetts; Schwarzenberger, Paul O., Louisiana State University Medical Center, New Orleans, Louisiana; Deisseroth, Albert, Yale University School of Medicine, New Haven, Connecticut; Blum, Ronald H., Beth Israel Medical, New York, New York; Lutzky, Jose, Mount Sinai Medical Center, Miami, Florida; and Wallach, Sabina R., Scripps Memorial Hospital, San Diego, La Jolla, and Encinitas, California; *Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 2-9-98. Not Selected for RAC Public Review: 8-28-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9802-234 (Closed) Gene Therapy/Phase III/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral Injection

Thompson, John A.; University of Washington, Seattle, Washington; Dreicer, Robert; the University of Iowa Hospitals and Clinics, Iowa City, Iowa; Seigler, Hilliard; Duke University Medical Center, Durham, North Carolina; Galanis, Evanthia; Mayo Clinic, Rochester, Minnesota; DeConti, Robert; H. Lee Moffitt Cancer Center, Tampa, Florida; Macdonald John S.; Saint Vincent's Hospital and Medical Center, New York, NY; Hutchins, Laura; University of Arkansas for Medical Sciences, Little Rock, Arkansas; Samlowski, Wolfram E.; the University of Utah Health Sciences Center, Salt Lake City, Utah; Bearden, James D.; Spartanburg Regional Medical Center, Spartanburg, South Carolina; Atkins, Michael B., Beth Israel Medical Center, Boston, Massachusetts; Gibbs, John and Oleksowicz, Leslie, Roswell Park Cancer Institute, Buffalo, New York; Schwarzenberger, Paul O., Louisiana State University Medical Center, New Orleans, Louisiana; Ernstoff, Marc, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; Campbell, Laura, Louisiana State University Medical Center, Shreveport, Louisiana; Levine, Edward, Wake Forest University Medical Center, Winston-Salem, North Carolina; Schuchter, Lynn M., University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania; Deisseroth, Albert, Yale University School of Medicine, New Haven, Connecticut; Paciucci, Paolo A., Mount Sinai Medical Center, New York, New York; Richart, John, Saint Louis University Health Sciences Center, St. Louis, Missouri; Meyskens Jr., Frank L., University of California, Irvine, Orange, California; Blum, Ronald H., Beth Israel Medical, New York, New York; Amatruda, Thomas, Virginia Piper Cancer Institute Abbott Northwestern Hospital, Minneapolis, Minnesota; Kuzel, Timothy, Northwestern Medical Faculty Foundation and Northwestern Memorial Hospital, Chicago, Illinois; Hawkins, Michael, Washington Cancer Institute, Washington, DC; Whitman, Eric D., The Melanoma Center of St. Louis, Saint Louis, Missouri; Cobb, Patrick, Billings Interhospital Oncology Project, Billings, Montana; Amin, Bipinkumar, Mid Dakota Clinic, Bismarck, North Dakota; Chowhan, Naveed, Cancer Care Center Incorporated, New Albany, Indiana; Lutzky, Jose, Mount Sinai Medical Center, Miami, Florida; Amatruda, Thomas, North Memorial Healthcare, Hubert H. Humphrey Cancer Center, Robbinsdale, Minnesota ;Patel, Ravi, Comprehensive Blood and Cancer Center, Bakersfield, California; Dobbs, Tracy W., Baptist Hospital of East Tennessee, Knoxville, Tennessee; Ahmed, Fakhiuddin, HemOnCare, P.C., Brooklyn, New York; Thant, Myo, Maryland Hematology/Oncology Associates, Baltimore, Maryland; Stark, James J., Maryview Medical Center, Portsmouth, Virginia; Arena, Francis, Arena Oncology Associates, Great Neck, New York; Brotherton, Timothy, Danville Hematology and Oncology, Inc. Danville Diagnostic Imaging Center, Danville, Virginia; Brouillard, Robert P., Scripps Memorial Hospital, La Jolla, Encinitas, and El Cajon, California; Polikoff, Jonathan A., Kaiser Permanente Medical Group, San Diego, California; Ritch, Paul S., Medical College of Wisconsin and Froedtert Memorial Lutheran Hospital, Milwaukee, Wisconsin; Bernstein, Joel I., Scripps Memorial Hospital, La Jolla, Encinitas, El Cajon, California; Richards, Jon, Lutheran General Hospital, Park Ridge, Illinois; and Giguere, Jeffrey, Hematology and Oncology Associates, Greenville, South Carolina; *A Controlled, Randomized Phase III Trial Comparing the Response to Dacarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 2-9-98. Not Selected for RAC Public Review: 7-20-98

9802-235 (Open) Gene Therapy/Phase I/Cancer/Brain Tumors/Glioblastoma/Vector-Directed Cell Lysis/In Vivo/Autologous Tumor Cells/Herpes Simplex Virus Type I/Tumor Lysis/Intratumoral Injection

Markert, James; University of Alabama, Birmingham, Alabama; and Medlock, Michael; Georgetown University Medical Center, Washington, D.C.; *A Dose Escalating Phase I Study of the Treatment of Malignant Glioma with G207, a Genetically Engineered HSV-1.* Sponsor: NeuroVir, Inc.

NIH/ORDA Receipt Date: 2-10-98. Publicly Reviewed at the June 18, 1998 RAC meeting

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9802-236 (Open) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/In Vivo/Autologous Tumor Cells/Adenovirus Type 5/Replication-competent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen/Intratumoral Injection

Simons, Jonathan W.; Johns Hopkins University School of Medicine, Baltimore, Maryland; *A Phase I Study of the Intraprostatic Injections of CN706, a Prostate-Specific Antigen Gene-Regulated Cytolytic Adenovirus, in Patients with Locally Recurrent Cancer Following Definitive Radiotherapy.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 2-13-98. Publicly Reviewed at the June 19, 1998 RAC meeting

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9802-237 (Closed) Gene Therapy/Phase I/Rheumatoid Arthritis/In Vivo/Autologous Synovial Cells/Naked Plasmid DNA/Herpes Simplex Virus Thymidine Kinase Gene/Ganciclovir/Intra-Articular Administration

Roessler, Blake J; The University of Michigan Medical Center, Ann Arbor, Michigan; *Molecular Synovectomy by In Vivo Gene Transfer: A Phase I Trial.*

NIH/ORDA Receipt Date: 2-13-98. Publicly Reviewed at the June 18, 1998 RAC meeting
Closed to new enrollment: 5-15-02; follow-up is continuing

9802-238 (Open) Gene Therapy/Phase I-II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Fibroblast Growth Factor (FGF) cDNA/Intracoronary Administration

Lee, Joon S.; University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; *Phase 1/2 Study of the Effects of Ascending Doses of Adenovirus Mediated Human FGF-4 Gene Transfer in Patients with Stable Exertional Angina.* Sponsor: Berlex Laboratories, Inc.

NIH/ORDA Receipt Date: 2-24-98. Publicly Reviewed at the June 18, 1998 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9802-239 (Closed) Gene Therapy/Phase I-II/Cancer/Hepatic Metastasis of Colorectal Carcinoma/Immunotherapy/In Vitro/Autologous CD4+ and CD8+ Lymphocytes/Retrovirus/CC49-Zeta T Cell Receptor/Hepatic Artery Infusion

Bergsland, Emily K.; University of California, San Francisco, San Francisco, California; *A Phase I/II Study of Hepatic Infusion of Autologous CC49-Zeta Gene-Modified T Cells in Patients with Hepatic Metastasis from Colorectal Cancer.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 2-25-98. Not Selected for RAC Public Review: 3-17-98

Notification from sponsor that trial is closed: 4-09-01

9803-240 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Pro-Drug/In Vivo/Autologous Tumor Cells/Adenovirus/ Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Rom, William N.; New York University School of Medicine, New York, New York; and Woo, Salvio L.C.; Mount Sinai School of Medicine, New York, New York; Phase *I Trial of Adenoviral Vector Delivery of the Herpes Simplex Thymidine Kinase Gene by Intratumoral Injection Followed by Intravenous Ganciclovir in Patients with Advanced Non-Small Cell Lung Cancer.*

NIH/ORDA Receipt Date: 3-3-98. Not Selected for RAC Public Review: 3-23-98

9803-241 (Closed) Gene Therapy/Phase I-II/Cancer/Chronic Myelogenous Leukemia/Multiple Myeloma/Non-Hodgkin's Lymphoma/Chronic Lymphocytic Leukemia/Adoptive Immunotherapy/In Vitro/Sibling Peripheral Blood Lymphocytes/Retrovirus/Herpes Simplex Virus Thymidine Kinase/Ganciclovir/Intravenous Infusion

Bensinger, William I.; University of Washington School of Medicine, Seattle, Washington; Parker, Pablo M.; City of Hope National Medical Center, Duarte, California; Henslee-Downey, Peggy J.; and Abhyankar, Sunil; Richland Memorial Hospital, University of South Carolina, Columbia, South Carolina; Giralt, Sergio; University of Texas, MD Anderson Cancer Center, Houston, Texas; Cornetta, Kenneth; Indiana University-Purdue University, Indianapolis, Indiana; and Carabasi, Matthew; The University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I/II Outpatient, Multicenter, Intrapatient, Multiple Dose Escalation Study of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Transduced Mononuclear Cells in Subjects with Persistent or Relapsed Chronic Myleogenous Leukemia, Chronic Lymphocytic Leukemia, Multiple Myeloma, and Non-Hodgkin's Lymphoma after HLA-Matched Sibling Allogeneic Stem Cell Transplant.* Sponsor: Chiron Corporation

NIH/ORDA Receipt Date: 3-27-98. Not Selected for RAC Public Review: 4-17-98
5-5-00: IND no longer active

9803-242 (Closed) Gene Therapy/Phase I/Cancer/Chronic Lymphocytic Leukemia/Immunotherapy/In Vitro/Autologous Leukemic Cells/Adenovirus/Serotype 5/CD 154 cDNA/Intravenous Infusion

Kipps, Thomas J.; University of California, San Diego, San Diego, California; *A Phase I Study of CD 154 Gene-Transduced Leukemia Cells in Patients with Chronic Lymphocytic Leukemia.*

NIH/ORDA Receipt Date: 3-30-98. Not Selected for RAC Public Review: 4-17-98

Notification from Immunogenex, now the sponsor of this trial, that study has been completed: 3-20-01

9804-243 (Open) Gene Therapy/Phase I/Other/Peripheral Arterial Disease/In Vivo/Ischemic Lower Limb/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Crystal, Ronald G.; Cornell University Medical College, New York, New York; Deitcher, Steven and Goldman, Corey, The Cleveland Clinic Foundation, Cleveland, Ohio; Rajagopalan, Sanjay, The University of Michigan, Ann Arbor, Michigan; Mohler III, Emile R., University of Pennsylvania Health System, Philadelphia, Pennsylvania; and Trachtenberg, Jeffrey, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; *Phase I Study of Direct Administration of a Replication Deficient Adenovirus vector ($Ad_{GV}VEGF121.10$) Containing the VEGF121 cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease.* Sponsor: Parke-Davis Pharmaceutical Research.

NIH/ORDA Receipt Date: 4-10-98. Not Selected for RAC Public Review: 4-30-98

9804-244 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Cationic Liposome Complex/Plasmid DNA/Interleukin-2 cDNA/Staphylococcus Enterotoxin B (SEB)/Intratumoral Injection

Walsh, Patrick; University of Colorado Health Sciences Center, Denver, Colorado; *A Phase I Study Using Direct Combination DNA Injections for the Immunotherapy of Metastatic Melanoma.*

NIH/ORDA Receipt Date: 4-10-98. Publicly Reviewed at the June 19, 1998 RAC meeting
Closed to enrollment, follow-up is continuing: 9-5-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9804-245 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) cDNA/Aerosol Administration

Moss, Richard; Stanford University School of Medicine, Palo Alto, California; Aitken, Moira, University of Washington Medical Center, Seattle, Washington; and Waltz, David, Harvard Medical School, Boston, Massachusetts; *A Phase I Study of Aerosolized tgAAVCF for the Treatment of Cystic Fibrosis Patients with Mild Lung Disease.* Sponsor: Targeted Genetics Corporation.

NIH/ORDA Receipt Date: 4-18-98. Not Selected for RAC Public Review: 12-3-98

9804-246 (Open) Gene Therapy/Phase II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Oncogene Regulation/HER-2/neu/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intratumoral Injection

Yoo, George H., Wayne State University School of Medicine, Detroit, Michigan; Villaret, Douglass B., University of Washington, Seattle, Washington; Gleich, Lyon, University of Cincinnati Medical Center, Cincinnati, Ohio; Hanna, Ehab, University of Arkansas Cancer Research Center, Little Rock, Arkansas; and Kenady, Daniel E., and Valentino, Joseph, University of Kentucky, Lexington, Kentucky; *A Multicenter Phase II Study of E1A Lipid Complex for the Intratumoral Treatment of Patients with Recurrent Head and Neck Squamous Cell Carcinoma.* Sponsor: Targeted Genetics Corporation.

NIH/ORDA Receipt Date: 4-18-98. Not Selected for RAC Public Review: 2-1-99

9804-247 (Open) Gene Therapy/Phase I/Monogenic Disease/Hemophilia A/In Vitro/Electroporation/Autologous Fibroblasts/Plasmid DNA/Factor VIII cDNA/Intraperitoneal Implantation

Roth, David A.; Beth Israel Deaconess Medical Center, Boston, Massachusetts; *A Phase I Safety Study of Autologous Transfected Human Fibroblasts Producing Human Factor VIII in Patients with Severe Hemophilia A.* Sponsor: Transkaryotic Therapies, Inc.

NIH/ORDA Receipt Date: 4-17-98. Publicly Reviewed at the June 19, 1998 RAC meeting

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9804-248 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Breast Cancer/Immunotherapy/In Vivo/Adenovirus/Serotype 5/B7.1 (CD80) cDNA/Intratumoral Injection

Schuchter, Lynn; University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *Phase I Trial of Therapeutic Cancer Vaccine Using Intratumoral Injections of B7-1 (H5.030CMVhB7) in Patients with Metastatic Melanoma or Metastatic Breast Cancer.*

NIH/ORDA Receipt Date: 4-23-98. Not Selected for RAC Public Review: 5-13-98

9804-249 (Open) Gene Therapy/Phase I/Cancer/Adenocarcinoma Expressing Carcinoembryonic Antigen (CEA)/In Vitro/Autologous T Lymphocytes/Retrovirus/anti-CEA-sFv-Zeta T Cell Receptor/Intravenous Infusion

Junghans, Richard Paul; Beth Israel Deaconess Medical Center, Boston, Massachusetts; *Phase I Study of T Cells Modified with Chimeric AntiCEA Immunoglobulin-T Cell Receptors (IgTCR) in Adenocarcinoma.*

NIH/ORDA Receipt Date: 4-28-98. Not Selected for RAC Public Review: 5-18-98

9804-250 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injections

Swisher, Steven; University of Texas M.D. Anderson Cancer Center/Texas Heart Institute, Houston, Texas; *An Efficacy Study of Adenoviral Vector Expressing Wildtype p53 (Ad5CMV-p53) Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer.* Sponsor: Aventis (formerly Gencell)

NIH/ORDA Receipt Date: 4-28-98. Not Selected for RAC Public Review: 5-18-98

9805-251 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/MUC -1/Interleukin-2/Intramuscular Injection

Figlin, Robert; University of California at Los Angeles, Los Angeles, California; *Phase I/II Trial of Antigen-Specific Immunotherapy in MUC-1 Positive Patients with Adenocarcinoma of the Prostate Using Vaccinia Virus-MUC1-IL2 (TG 1031).* Sponsor: Transgene, S.A.

NIH/ORDA Receipt Date: 5-1-98. Not Selected for RAC Public Review: 5-22-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9805-252 (Open) Gene Therapy/Phase I/Cancer/Colorectal/In Vitro/Allogeneic Tumor Cells and Fibroblasts/Lethally Irradiated/Plasmid DNA/Interleukin-2 cDNA/B7.1 (CD80)/Subcutaneous Injection

Sobol, Robert E.; Sidney Kimmel Cancer Center, San Diego, California; *A Phase I Study of Allogeneic Tumor Cells Genetically Modified to Express B7.1 (CD80) Mixed with Allogeneic Fibroblasts Genetically Modified to Secrete IL-2 in Patients with Colorectal Carcinoma.*

NIH/ORDA Receipt Date: 5-7-98. Not Selected for RAC Public Review: 5-27-98

9805-253 (Closed) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD8+ T Cells/ Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous Infusion

Scadden, David T.; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts; Mitsuyasu, Ronald; University of California, Los Angeles, Los Angeles, California; and Deeks, Steven; University of California, San Francisco, San Francisco, California; *A Phase II Study of Autologous CD4-Zeta Gene-Modified T Cells in HIV Infected Patients with Undetectable Plasma Viremia on Highly Active Anti-Retroviral Drug Therapy* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 5-14-98. Not Selected for RAC Public Review: 6-3-98

Study closed to new accrual, follow-up is continuing: 7-13-01

9805-254 (Open) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Naked Plasmid/gp 100 Melanoma Antigen/Intradermal or Intramuscular Injection

Rosenberg, Steven A.; National Institutes of Health, Bethesda, Maryland; *Immunization of Patients with Metastatic Melanoma Using DNA Encoding the GP100 Melanoma Antigen.* Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-4-98. Not Selected for RAC Public Review: 6-24-98

9806-255 (Closed) Gene Therapy/Phase I/Cancer/Ovarian/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intraperitoneal Administration

Muller, Carolyn Y.; University of Texas Southwestern Medical School, Dallas, Texas; *Phase I Trial of Intraperitoneal Adenoviral p53 Gene Therapy in Patients with Advanced Recurrent or Persistent Ovarian Cancer.* Sponsor: National Cancer Institute - Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 6-2-98. Not Selected for RAC Public Review: 6-22-98
Closed to accrual: 4-15-02

9806-256 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intradermal and Subcutaneous Injections

Suzuki, Tsuneo; University of Kansas Medical Center, Kansas City, Kansas; *Autologous, Irradiated, Melanoma Cells Transduced Ex Vivo with an Adenovirus Vector (Adv/GM-CSF) Expressing Granulocyte-Macrophage Colony Stimulating Factor Gene.*

NIH/ORDA Receipt Date: 6-3-98. Not Selected for RAC Public Review: 6-23-98

9806-257 (Open) Gene Therapy/Phase I/Cancer/Breast/Colon/Head and Neck/Soft Tissue Sarcoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Lethally Irradiated/ Adenovirus/Serotype 5/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intradermal and Subcutaneous Injections

Suzuki, Tsuneo; University of Kansas Medical Center, Kansas City, Kansas; *Autologous, Irradiated, Cancer Cells (Breast Cancer, Colon Cancer, Head and Neck Cancer, and Soft Tissue Sarcoma) Transduced Ex Vivo with an Adenovirus Vector (Adv/GM-CSF) Expressing Granulocyte-Macrophage Colony Stimulating Factor Gene.*

NIH/ORDA Receipt Date: 6-3-98. Not Selected for RAC Public Review: 6-23-98

9806-258 (Open) Gene Therapy/Phase I/ Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Crystal, Ronald G.; Cornell University Medical College, New York, New York; *Phase I Study of Direct Administration of a Replication Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease Via Minimally Invasive Surgery.* Sponsor: Parke-Davis Pharmaceutical Research.

NIH/ORDA Receipt Date: 6-8-98. Not Selected for RAC Public Review: 8-13-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9806-259 (Closed) Gene Therapy/Phase II/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1102/Interleukin-2 cDNA/Intratumoral Injection

Figlin, Robert; University of California at Los Angeles, Los Angeles, California; Thompson, John, A.; University of Washington, Seattle, Washington; Galanis, Evanthia; Mayo Clinic, Rochester, Minnesota; and Bukowski, Ronald, Cleveland Clinic Foundation, Cleveland, Ohio; *Phase II Study of Direct Gene Transfer of IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Renal Cell Carcinoma.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 6-15-98. Not Selected for RAC Public Review: 7-6-98

9806-260 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical-1005/HLA-B7/Beta 2-Microglobulin cDNA/Concurrent Interleukin-2 Injection/Direct Intratumoral Injection

Hersh, Evan; Arizona Cancer Center, Tucson, Arizona; *Phase I Study of HLA-B7/β2M Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) by Direct Gene Transfer with Concurrent Low-Dose Subcutaneous IL-2 Protein Therapy as an Immunotherapeutic Regimen in Malignant Melanoma.*

NIH/ORDA Receipt Date: 6-26-98. Not Selected for RAC Public Review: 7-16-98

9806-261 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/Retrovirus/Transdominant Rev or Rev and Antisense Pol 1/Intravenous Infusion

Amado, Rafael G.; University of California at Los Angeles, Los Angeles, California; and Yuen, Alan R.; Stanford University Medical Center; Stanford, California; Scadden, David T., Massachusetts General Hospital, Boston, Massachusetts; Lill, Michael, Cedars-Sinai Medical Center, Los Angeles, California; and Carabasi, Matthew, University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I/II Study of the Safety and Feasibility of RevM10 or RevM10/Antisense Pol 1 Transduced Hematopoietic Stem Cells (HSC) in HIV-1 Related Non-Hodgkin's Lymphoma Patients Already Being Treated with High Dose Chemotherapy and Peripheral Blood Stem Cell Support.* Sponsor: Systemix, Inc.

NIH/ORDA Receipt Date: 6-30-98. Not Selected for RAC Public Review: 7-20-98

9807-262 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intraperitoneal Administration

Wolf, Judith K.; The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I Study of Ad-p53 (NSC#683550) for Patients with Platinum- and Paclitaxel-Resistant Epithelial Ovarian Cancer.*

NIH/ORDA Receipt Date: 7-24-98. Not Selected for RAC Public Review: 8-13-98

9808-263 (Open) Gene Therapy/Phase I/Cancer/Malignant Glioma/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Lang, Frederick F., Jr. and Yung, W. K. Alfred; The University of Texas MD Anderson Cancer Center, Houston, Texas; and Greenberg, Harry, University of Michigan, Ann Arbor, Michigan; *Phase I Trial of Adenovirus-Mediated Wild Type p53 Gene Therapy for Malignant Gliomas.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 8-13-98. Not Selected for RAC Public Review: 9-2-98

9808-264 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vivo/Vaccinia Virus/MUC-1/Interleukin-2/Intramuscular Injection

Gitlitz, Barbara J.; University of California Los Angeles, Los Angeles, California; *Phase I/II Trial of Antigen-Specific Immunotherapy in MUC-1 Positive Patients with Advanced Non-Small Cell Lung Cancer Using Vaccinia-Virus-MUC1-IL2 (TG1031).* Sponsor: Transgene, S.A.

NIH/ORDA Receipt Date: 8-27-98. Not Selected for RAC Public Review: 9-18-98

9809-265 (Open) Gene Therapy/Phase I/Cancer/Solid Tumors/Chemoprotection/In Vitro/Peripheral Blood CD34+ Cells/Retrovirus/O^6-Methylguanine DNA Methyltransferase cDNA/Intravenous Infusion

Gerson, Stanton L.; Case Western Reserve University, Cleveland, Ohio; *Mutant MGMT Gene Transfer Into Human Hematopoietic Progenitors to Protect Hematopoiesis During O^6-Benzylguanine (BG, NSC 637037) and BCNU Therapy of Advanced Solid Tumors.*

NIH/ORDA Receipt Date: 9-2-98. Not Selected for RAC Public Review: 9-23-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9809-266 (Open) Gene Therapy/Phase I-II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Human Interferon-alpha cDNA/Intratumoral Injection

McQuone, Shelly J.; The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *A Multi-Center, Open-Label, Multiple Administration, Rising Dose Study of the Safety, Tolerability, and Efficacy of IFN-alpha Gene Medicine in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: GeneMedicine, Inc.

NIH/ORDA Receipt Date: 9-22-98. Not Selected for RAC Public Review: 3-19-99

9810-267 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Morris, John C.; National Institutes of Health, Bethesda, Maryland; *A Phase I Study of Intralesional Administration of an Adenovirus Vector Expressing the HSV-1 Thymidine Kinase Gene (AdV.RSV-TK) in Combination with Escalating Doses of Ganciclovir in Patients with Cutaneous Metastatic Malignant Melanoma.*

NIH/ORDA Receipt Date: 10-6-98. Not Selected for RAC Public Review: 10-27-98

9810-268 (Closed) Gene Therapy/Phase I/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Irradiated/Adenovirus/Serotype 5/B7.1 (CD80) cDNA/Subcutaneous Injection

Antonia, Scott J.; University of South Florida, Tampa, Florida; *Treatment of Patients with Stage IV Renal Cell Carcinoma with B7-1 Gene-Modified Autologous Tumor Cells and Systemic IL-2.*

NIH/ORDA Receipt Date: 10-26-98. Not Selected for RAC Public Review: 11-30-98

Closed to new accrual: 3-29-01

9811-269 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/Type 5/MART-1 Melanoma Antigen/Intravenous or Intradermal Injection

Economou, James S., UCLA Medical Center, Los Angeles, California; *A Phase I Trial Testing MART-1 Genetic Immunization in Malignant Melanoma.*

NIH/ORDA Receipt Date: 11-17-98. Not Selected for RAC Public Review: 12-8-98

9811-270 (Closed) Gene Therapy/Phase II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/Beta2-Microglobulin cDNA/Direct Intratumoral Injection

Hanna, Ehab, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Wagman, Lawrence D., City of Hope National Medical Center, Duarte, California; Gluckman, Jack L., University of Cincinnati Medical Center, Cincinnati, Ohio; and Wolf, Gregory T., University of Michigan Medical Center, Ann Arbor, Michigan; *Phase II Study of the Safety, Efficacy, and Effect on Quality of Life of Allovectin-7 Immunotherapy for the Treatment of Recurrent or Persistent Squamous Cell Carcinoma of the Head and Neck.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 11-19-98. Not Selected for RAC Public Review: 2-5-99

9811-271 (Closed) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with Moderate-Risk Critical Limb Ischemia.* Sponsor: Vascular Genetics, Inc.

NIH/ORDA Receipt Date: 11-23-98. Not Selected for RAC Public Review: 12-14-98
Follow-up has been completed: 11-29-01

9811-272 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy/In Vivo/Vaccinia Virus/MUC-1/Intradermal Injection

Kufe, Donald W., Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Trial of Recombinant Vaccinia Virus that Expresses DF3/MUC1 in Patients with Metastatic Adenocarcinoma of the Breast.*

NIH/ORDA Receipt Date: 11-23-98. Not Selected for RAC Public Review: 12-24-98

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9812-273 (Open) Gene Therapy/Phase I-II/Infectious Diseases/Human Immunodeficiency Virus-1 (HIV-1)/In Vitro/Immunotherapy/Autologous CD8+ HIV-Specific T Cells/Retrovirus/Neomycin Phosphotransferase Gene/Intravenous Infusion

Riddell, Stanley R., Fred Hutchinson Cancer Research Center, Seattle, Washington; *The Safety and Antiviral Efficacy of Cellular Adoptive Immunotherapy with Autologous CD8+ HIV-Specific Cytotoxic T Cells Combined with Interleukin-2 for HIV Seropositive Individuals.*

NIH/ORDA Receipt Date: 12-3-98. Not Selected for RAC Public Review: 1-5-99

9812-274 (Closed) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Fibroblast Growth Factor (FGF) cDNA/Intramuscular Injection

Comerota, Anthony J., Temple University School of Medicine, Philadelphia, Pennsylvania; Laird, John R., Washington Hospital Center, Washington, D.C.; Sequeira, Rafael F., University of Miami, School of Medicine, Miami, Florida; Henry, Timothy, Hennepin County Medical Center, Minneapolis, Minnesota; and Chronos, Nicholas, Atlanta Cardiology Group, Atlanta, Georgia; *A Phase I, Multi-Center, Open Label, Safety and Tolerability Study of Increasing Single Dose of NV1FGF Administered by Intra-Muscular Injection in Patients with Severe Peripheral Artery Occlusive Disease.* Sponsor: Aventis (formerly Gencell).

NIH/ORDA Receipt Date: 12-17-98. Not Selected for RAC Public Review: 2-4-99

9812-275 (Open) Gene Therapy/Phase I/Cancer/Advanced Malignancies/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intravenous Injection

Eckhardt, S. Gail, Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, Texas; *A Pharmacokinetic, Safety and Tolerability Study of Intravenous INGN in Patients with Advanced Cancer.* Sponsor: Introgen Therapeutics, Inc.

NIH/ORDA Receipt Date: 12-18-98. Not Selected for RAC Public Review: 5-13-99

9812-276 (Open) Gene Therapy/Phase I/Cancer/Prostate/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Valacyclovir/Intratumoral Injection

Gardner, Thomas A. and Chung, Leland W. K., University of Virginia Health, Charlottesville, Virginia; *Phase I Study of Ad-OC-TK Plus Valacyclovir for the Treatment of Metastatic or Recurrent Prostate Cancer.*

NIH/ORDA Receipt Date: 12-23-98. Not Selected for RAC Public Review: 1-14-99

9812-277 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/Retrovirus/Transdominant Rev/Antisense Pol 1/Intravenous Infusion

Amado, Rafael G., University of California, Los Angeles, Los Angeles, California; Carabasi, Matthew, University of Alabama at Birmingham, Birmingham, Alabama; Swindells, Susan, University of Nebraska Medical Center, Omaha, Nebraska; and Scadden, David T., Massachusetts General Hospital, Boston, Massachusetts; *A Phase I/II Study in HIV-1 Infected Patients Infused with CD34+Thy1+ Hematopoietic Stem Cells (HSC) from G-CSF Mobilized Peripheral Blood Retrovirally Transduced with RevM10 or RevM10/Antisense Pol1.* Sponsor: Systemix, Inc.

NIH/ORDA Receipt Date: 12-28-98. Not Selected for RAC Public Review: 1-19-99

9901-278 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Plasmid DNA/MART-1 Melanoma Antigen/Intramuscular Injection

Conry, Robert M., University of Alabama at Birmingham, Birmingham, Alabama; *Phase I Dose Escalation Trial of Polynucleotide Immunization with Plasmid DNA Encoding MART-1 (Melanoma Antigen Recognized by T Cells-1) in Patients with Resected Melanoma at Significant Risk for Relapse.*

NIH/ORDA Receipt Date: 1-4-99. Not Selected for RAC Public Review: 1-25-99

9901-279 (Open) Gene Therapy/Phase I/Monogenic Disease/Hemophilia B/In Vivo/Adeno-Associated Virus/Factor IX Gene/Intramuscular Injection

Manno, Catherine S., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *A Phase I Safety Study in Patients with Severe Hemophilia B (Factor IX Deficiency) Using Adeno-Associated Viral Vector to Deliver the Gene for Human Factor IX to Skeletal Muscle.* Sponsor: Avigen.

NIH/ORDA Receipt Date: 1-7-99. Publicly Reviewed at the March 12, 1999 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9901-280 (Open) Gene Therapy/Phase II-III/Cancer/Ovarian/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intraperitoneal Administration

Buller, Richard, The University of Iowa Hospitals and Clinics, Iowa City, Iowa; Carson, Linda F., University of Minnesota, Minneapolis, Minnesota; Weisberg, Tracey, Maine Center for Cancer Medicine, Scarborough, Maine; Christopherson, Wayne A., Mercy Hospital of Pittsburgh, Pittsburgh, Pennsylvania; Molpus, Kelly, University of Nebraska Medical Center, Omaha, Nebraska; Davidson, Susan A., University of Colorado Health Sciences Center, Denver, Colorado; Gutheil, John C., Sharp HealthCare, Sidney Kimmel Cancer Center, San Diego, California; Bloss, Jeffrey D., University of Missouri, Columbia, Missouri; Blum, Ronald, Beth Israel Medical Center, New York, New York; Puls, Larry E., Greenville Hospital System, Greenville, South Carolina; Teng, Nelson Nan-Hsiung, Stanford University School of Medicine, Stanford, California; Pergram, Mark D., University of California, Los Angeles, Los Angeles, California; Ueland, Federick, University of Kentucky Medical Center, Lexington, Kentucky; Rodriguez, Michael, University Hospitals of Cleveland, Cleveland, Ohio; Malfetano, John H., Albany Medical College, Albany, New York; Edwards, Robert P., University of Pittsburgh, Pittsburgh, Pennsylvania; Rader, Janet, Washington University, Saint Louis, Missouri; Benigno, Benedict B., Northside Hospital, Atlanta, Georgia; Lucci, Joseph T., University of Texas Medical Branch, Galveston, Texas; Delmore, James E., University of Kansas School of Medicine, Wesley Medical Center, Wichita, Kansas; Smith, Harriet O., University of New Mexico School of Medicine, Albuquerque, New Mexico; Bristow, Robert E., Johns Hopkins School of Medicine, Baltimore, Maryland; Abbas, Fouad, Sinai Hospital of Baltimore, Baltimore, Maryland; Fort, Giles, Woman's Hospital, Baton Rouge, Louisiana; Berchuck, Andrew, Duke University Medical Center; Coleman, Robert, University of Texas Southwestern Medical Center, Dallas, Texas; Rocereto, Thomas, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Camden, New Jersey; Hall, James, Carolinas Medical Center, Charlotte, North Carolina; Holloway, Robert, Walt Disney Memorial Cancer Institute, Orlando, Florida; Garcia, Agustin, University of Southern California, Norris Cancer Hospital, Los Angeles, California; Lentz, Samuel Wake Forest University School of Medicine, Winston-Salem, North Carolina; Swensen, Ron, Loma Linda University Cancer Institute, Loma Linda, California; Horowitz, Ira, Emory University School of Medicine, Atlanta, Georgia; Kline, Richard and Burroff, Janet, Alton Ochsner Medical Foundation, New Orleans, Louisiana; Scudder, Sidney, University of California, Davis, Sacramento, California; Noubisi, Boniface, University of Florida, Gainesville, Florida; and Celano, Paul, Greater Baltimore Medical Center, Baltimore, Maryland; *A Phase II/III Trial of Chemotherapy Alone Versus Chemotherapy Plus SCH 58500 in Newly Diagnosed Stage III Ovarian and Primary Peritoneal Cancer Patients with ≥0.5 cm and ≤2 cm Residual Disease Following Surgery.* Sponsor: Schering Corporation

NIH/ORDA Receipt Date: 1-12-99. Not Selected for RAC Public Review: 6-2-99

9901-281 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/Type 5/MART-1 Melanoma Antigen/gp 100 Melanoma Antigen/Subcutaneous Injection

Haluska, Frank, Harvard Medical School, Boston, Massachusetts and Nemunaitis, John J., US Oncology, Dallas, Texas; *Phase I/II Trial of the Safety, Immunogenicity, and Efficacy of Autologous Dendritic Cells Transduced with Adenoviruses Encoding the MART-1 and gp100 Melanoma Antigens Administered With or Without Low Dose Recombinant Interleukin-2 (rIL-2) in Patients with Stage IV Melanoma.* Sponsor: Genzyme Molecular Oncology.

NIH/ORDA Receipt Date: 1-12-99. Not Selected for RAC Public Review: 3-30-99

9901-282 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen/Intramuscular Injection

Eder, Joseph Paul, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase II Randomized Trial of Recombinant Fowlpox and Recombinant Vaccinia Virus Expressing PSA in Patients with Adenocarcinoma of the Prostate.* Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP).

NIH/ORDA Receipt Date: 1-12-99. Not Selected for RAC Public Review: 1-24-00

9901-283 (Closed) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Small, Eric J., University of California, San Francisco, San Francisco, California; *Phase I/II Study of a Prime-Boost Schedule of Human GM-CSF Gene Transduced Irradiated Prostate Allogeneic Cancer Cell Vaccines (Allogeneic Prostate GVAX™) in Hormone-Naive Prostate Cancer Patients.* Sponsor: Cell Genesys

NIH/ORDA Receipt Date: 1-22-99. Not Selected for RAC Public Review: 2-11-99

Notification from sponsor that trial is closed: 4-09-01

9902-284 (Open) Gene Therapy/Phase I/Monogenic Disease/Hemophilia A/In Vivo/Retrovirus/Factor VIII cDNA/Intravenous Infusion

Ragni, Margret V., University of Pittsburgh, Pittsburgh, Pennsylvania; Lusher, Jeanne M., Children's Hospital of Michigan, Detroit, Michigan; Powell, Jerry S., University of California, Davis, Medical Center, Sacramento, California; White, Gilbert, University of North Carolina School of Medicine, Chapel Hill, North Carolina and Ewenstein, Bruce M., Brigham and Women's Hospital, Boston, Massachusetts; *Phase I Multi-Center, Single Treatment Dose Escalation Study of Factor VIII Vector [HFVIII(V)] for Treatment of Severe Hemophilia A.* Sponsor: Chiron Corporation

NIH/ORDA Receipt Date: 2-5-99. Publicly Reviewed at the September 3, 1999 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9902-285 (Open) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell Carcinoma/In Vivo/Cationic Liposome Complex with DC-Chol/Epidermal Growth Factor Receptor Antisense/Intratumoral Injection

Grandis, Jennifer Rubin, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; *A Phase I Trial of Intratumoral Antisense EGFR DNA and DC-Chol Liposomes in Advanced Oral Squamous Cell Carcinoma.*

NIH/ORDA Receipt Date: 2-12-99. Not Selected for RAC Public Review: 3-5-99

9902-286 (Open) Gene Therapy/Phase I/Cancer/Lung, Head and Neck/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1005/HLA-B7/Beta 2-Microglobulin cDNA/Concurrent Interleukin-2 Injection/Direct Intratumoral Injection

Stopeck, Alison, Arizona Cancer Center, University of Arizona, Tucson, Arizona; *Phase I Study of HLA-B7/beta2M Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) by Direct Gene Transfer with Concurrent Low-Dose Subcutaneous IL-2 Protein Therapy as an Immunotherapeutic Regimen in Lung and Head and Neck Cancers.* Sponsor: Vical Inc.

NIH/ORDA Receipt Date: 2-16-99. Not Selected for RAC Public Review: 3-8-99

9902-287 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Bronchoalveolar Lavage

Schiller, Joan, University of Wisconsin, Madison, Wisconsin; and Carbone, David, P., Vanderbilt University Medical Center, Nashville, Tennessee; *Phase I Pilot Trial of Adenovirus p53 in Bronchioloalveolar Cell Lung Carcinoma (BAC) Administered by Bronchoalveolar Lavage.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 2-16-99. Not Selected for RAC Public Review: 3-25-99

9902-288 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection (Endobronchial or Percutaneous)

Schiller, Joan, University of Wisconsin, Madison, Wisconsin; *Phase I Pilot Trial of Adenovirus p53 and Radiotherapy on Non-Small Cell Lung Cancer.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 2-18-99. Not Selected for RAC Public Review: 6-24-99

9902-289 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Nasal Epithelial Cells/Cationic Liposome Complex/Alpha-1 Antitrypsin cDNA/Intranasal Administration

Brigham, Kenneth L., Vanderbilt University School of Medicine, Nashville, Tennessee; *Expression of an Exogenously Delivered Human Alpha-1 Antitrypsin Gene in Nasal Epithelium of Patients with Cystic Fibrosis.*

NIH/ORDA Receipt Date: 2-19-99. Not Selected for RAC Public Review: 4-2-99

9902-290 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Particle Mediated Gene Transfer (Accel®)/Plasmid DNA/gp 100 cDNA/Granulocyte-Macrophage Colony Stimulating Factor cDNA

Albertini, Mark R., University of Wisconsin, Madison, Wisconsin; *Phase I Trial of Immunization Using Particle-Mediated Transfer of Genes for GP-100 and GM-CSF into Uninvolved Skin of Patients with Melanoma.*

NIH/ORDA Receipt Date: 2-22-99. Not Selected for RAC Public Review: 3-15-99
3-29-00: Closed to accrual and treatment; follow-up will continue

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9902-291 (Open) Gene Therapy/Phase I/Monogenic Disease/Fanconi Anemia/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Fanconi Anemia Complementation Group A cDNA/Intravenous

Walsh, Christopher E., The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; *Retroviral-Mediated Gene Transfer of the Fanconi Anemia Group A Gene into Hematopoietic Progenitor Cells of Group A Patients.*

NIH/ORDA Receipt Date: 2-22-99. Not Selected for RAC Public Review: 3-15-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9902-292 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/gp 100 Melanoma Antigen/Intramuscular or Intravenous Injection

Rosenberg, Steven A., National Institutes of Health, Bethesda, Maryland; *Immunization of Patients with Metastatic Melanoma Using a Recombinant Fowlpox Virus Encoding a GP 100 Peptide Preceded by an Endoplasmic Reticulum Insertion Signal Sequence.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 2-24-99. Not Selected for RAC Public Review: 3-22-99

9902-293 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen/Intramuscular or Intradermal Injection

Kaufman, Howard, Albert Einstein College of Medicine, Bronx, New York; *Phase II Randomized Study of Vaccine Treatment of Advanced Prostate Cancer.* Sponsor: Eastern Cooperative Oncology Group

NIH/ORDA Receipt Date: 2-24-99. Not Selected for RAC Public Review: 8-13-99

9902-294 (Closed) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Administration

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts, Henry, Timothy D., Hennepin County Medical Center, Minneapolis, Minnesota and Schatz, Richard A., Scripps Clinic, La Jolla, California; *A Multicenter, Open-Label, Dose-Escalating Study of Intramyocardial Vascular Endothelial Growth Factor 2 (VEGF-2) Gene Therapy in Refractory Patients with Stable Exertional Angina Who Are Not Candidates for Revascularization Procedures.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 2-26-99. Not Selected for RAC Public Review: 6-11-99

9903-295 (Withdrawn from RAC Review) Gene Therapy/Phase I/Monogenic Disease/Gyrate Atrophy/In Vitro/Autologous Keratinocytes/Retrovirus/Ornithine Aminotransferase (OAT) cDNA/Skin Patch Administration

Nussenblatt, Robert B., National Institutes of Health, Bethesda, Maryland; *Phase I Study in the Safety and Efficacy of Transduced Keratinocytes for Possible Treatment of Gyrate Atrophy.*

NIH/ORDA Receipt Date: 3-4-99. Withdrawn from RAC review: 9-18-00

9903-296 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Human Gamma Interferon cDNA/Intratumoral Injection

Rosenblatt, Joseph D., University of Rochester Medical Center, Rochester, New York; *Phase I Trial of Immunotherapy with Adenovirus-Interferon-Gamma (TG1041) in Patients with Malignant Melanoma.* Sponsor: Transgene, Inc.

NIH/ORDA Receipt Date: 3-10-99. Not Selected for RAC Public Review: 3-30-99

Closed by sponsor to further enrollment: 06-29-01

9903-297 (Open) Gene Marking/Autoimmune Disease/Multiple Sclerosis/In Vitro/CD34+ Autologous Peripheral Blood/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Infusion

Krance, Robert, Baylor College of Medicine, Houston, Texas; *Intensive Immunosuppression Followed by Rescue with CD34 Selected, T Cell Depleted, Leukopheresis Products in Patients with Multiple Sclerosis.*

NIH/ORDA Receipt Date: 3-24-99. Not Selected for RAC Public Review: 4-21-99

9903-298 (Open) Gene Therapy/Phase II/Cancer/Ovarian/Pro-Drug/In Vivo/PA317/Retrovirus/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intraperitoneal/Catheter

Link, Charles J., and Morrman, Donald, Human Gene Therapy Research Institute, Des Moines, Iowa; *A Phase II Trial of In Vivo Gene Therapy with the Herpes Simplex Thymidine Kinase for the Treatment of Ovarian Cancer.*

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9903-299 (Open) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts, Baumgartner, Iris, Bern University, Bern Switzerland and Olin, Jeffrey Wayne, Cleveland Clinic Foundation, Cleveland, Ohio; *A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with Moderate-Risk Critical Limb Ischemia.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99

9903-300 (Closed) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with High-Risk Critical Limb Ischemia.*

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99
Follow-up has been completed: 11-29-01

9903-301 (Open) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts, Baumgartner, Iris, Bern University, Bern Switzerland and Olin, Jeffrey Wayne, Cleveland Clinic Foundation, Cleveland, Ohio; *A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with High-Risk Critical Limb Ischemia.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99

9903-302 (Closed) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Open-Label, Rescue-Therapy Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with Moderate-Risk or High-Risk Critical Limb Ischemia.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 3-26-99. Not Selected for RAC Public Review: 4-15-99
Follow-up is complete: 11-29-01

9903-303 (Closed) Gene Marking/Cancer/Neuroblastoma/Sarcoma/Retinoblastoma/In Vitro/CD34+ Autologous Peripheral Blood or Bone Marrow/Dihydrofolate Reductase cDNA/Intravenous Infusion

Cunningham, John M., St. Jude Children's Research Hospital, Memphis, Tennessee; *Tumor Purging of Autologous Stem Cell Grafts in Children with High-Risk Solid Tumors: Transplantation of Retrovirally Marked Stem Cell Grafts Purified by CD34+ Antibody Selection and High-Speed Cell Sorting.*

NIH/ORDA Receipt Date: 3-29-99. Not Selected for RAC Public Review: 5-18-99
Closed: 11-4-02

9904-304 (Open) Gene Therapy/Phase I/Cancer/Retinoblastoma/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection (Intraocular Tumor)

Hurwitz, Richard L., Baylor College of Medicine, Houston, Texas; *Pediatric Phase I Study of AdV/RSV-TK Followed by Ganciclovir for Retinoblastoma*

NIH/ORDA Receipt Date: 4-1-99. Publicly Reviewed at the June 14, 1999 RAC meeting

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9904-305 (Open) Gene Therapy/Phase I/Cancer/Breast/Tumor Suppressor Gene/In Vitro/Autologous CD34+ Cells/Adenovirus/Serotype 5/p53 cDNA/Intravenous Infusion

Baynes, Roy D., Karmanos Cancer Institute, Wayne State University, Detroit, Michigan; *A Phase I Study of Infused Mobilized, Autologous Peripheral Blood Progenitor Cells, Which Have Been Incubated with a Recombinant Adenovirus-Wild-Type p53 Construct (SCH 58500) to Purge Any Contaminating Breast Cancer Cells, As Stem Cell Support After High-Dose Chemotherapy in Patients with Breast Cancer Metastatic to Bone and Bone Marrow.*

NIH/ORDA Receipt Date: 4-5-99. Not Selected for RAC Public Review: 5-3-99

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9904-306 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Prostate Specific Antigen/Intravenous

Vieweg, Johannes, Duke University Medical Center, Durham North Carolina; *Safety and Feasibility Study of Active Immunotherapy in Patients with Hormone Refractory Prostate Cancer Using Autologous Dendritic Cells Pulsed with RNA Encoding Prostate Specific Antigen, PSA*

NIH/ORDA Receipt Date: 4-6-99. Not Selected for RAC Public Review: 4-26-99

9904-307 (Closed) Gene Therapy/Phase I/Cancer/Cervical/Immunotherapy/In Vivo/Vaccinia Virus/Human Papilloma Virus E6 and E7/Interleukin-2/Intramuscular Injection

Kaufman, Raymond H., Baylor College of Medicine, Houston, Texas; *Phase I Trial of Immunotherapy with MVA-HPV-IL2 (TG4001) in Women with Cervical Intraepithelial Neoplasia (CIN) Grade 3.* Sponsor: Transgene, Inc.

NIH/ORDA Receipt Date: 4-8-99. Not Selected for RAC Public Review: 4-26-99

9904-308 (Open) Gene Therapy/Phase I/Cancer/Leukemia/Adoptive Immunotherapy/In Vitro/Donor CD8+ Lymphocytes/Retrovirus/Hygromycin Phosphotransferase-Herpes Simplex Thymidine Kinase Fusion Gene/Intravenous Infusion

Warren, Edus, Fred Hutchinson Cancer Research Center, Seattle, Washington; *Phase I Study of Adoptive Immunotherapy with Gene-Modified and Unmodified CD8+ Minor Histocompatibility (H) Antigen-Specific CTL Clones for Patients with Relapse of AML or ALL After Allogeneic Hematopoietic Stem Cell Transplant.*

NIH/ORDA Receipt Date: 4-13-99. Not Selected for RAC Public Review: 5-3-99

9904-309 (Closed) Gene Therapy/Phase I/Cancer/Cervical Cancer/Immunotherapy/In Vivo/Vaccinia Virus/Human Papilloma Virus E6 and E7/Interleukin-2/Intramuscular Injection

Goff, Barbara A., University of Washington School of Medicine, Seattle, Washington; *Phase I Trial of Immunotherapy with MVA-HPV-IL2 (TG4001) in Women with Advanced Cervical Carcinoma.* Sponsor: Transgene, Inc.

NIH/ORDA Receipt Date: 4-22-99. Not Selected for RAC Public Review: 5-12-99

9904-310 (Open) Gene Marking/Osteodysplasia/In Vitro/Stromal Cells for Donor Bone Marrow/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Infusion

Horwitz, Edwin M., St. Jude Children's Research Hospital, Memphis, Tennessee; *Stromal Therapy of Osteodysplasia After Allogeneic Bone Marrow Transplantation: A Phase I Study.*

NIH/ORDA Receipt Date: 4-22-99. Not Selected for RAC Public Review: 5-12-99

9904-311 (Open) Gene Marking/Cancer/Neuroblastoma/In Vitro/Autologous Cytotoxic T-Lymphocytes from Peripheral Blood/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Infusion

Nuchtern, Jed, Baylor College of Medicine, Houston, Texas; *Administration of Neomycin Resistance Gene Marked Neuroblastoma Specific Cytotoxic T-Lymphocytes to Patients with Relapsed/Resistant Neuroblastoma.*

NIH/ORDA Receipt Date: 4-30-99. Not Selected for RAC Public Review: 5-20-99

9905-312 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1102/Leuvectin/Interleukin-2 cDNA/Intratumoral Injection

Belldegrun, Arie, University of California, Los Angeles, Los Angeles, California; Klein, Eric, Cleveland Clinic Foundation, Cleveland, Ohio; Corman, John, VA Puget Sound Health Care System, Seattle, Washington; and Moul, Judd, Walter Reed Army Medical Center, Washington, DC; *Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer.* Sponsor: Vical, Inc.

NIH/ORDA Receipt Date: 5-7-99. Not Selected for RAC Public Review: 5-27-99

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9905-313 (Open) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/Vaccinia Virus/Tyrosinase cDNA/Intramuscular Injection

Topalian, Suzanne L., National Institutes of Health, Bethesda, Maryland; *Immunization of Patients with Metastatic Melanoma Using Recombinant Fowlpox and Vaccinia Viruses Encoding the Tyrosinase Antigen.*

NIH/ORDA Receipt Date: 5-11-99. Not Selected for RAC Public Review: 6-1-99

9905-314 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Vaccinia Virus/B7.1 (CD80)/Intratumoral Injection

Kaufman, Howard L., Columbia University, New York, New York; *A Phase I Trial of Intralesional RV-B7.1 Vaccine in the Treatment of Malignant Melanoma.* Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)

NIH/ORDA Receipt Date: 5-12-99. Not Selected for RAC Public Review: 7-23-99
Closed: 5-15-02; follow-up is continuing

9905-315 (Closed) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Retrovirus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Small, Eric J., University of California, San Francisco, San Francisco, California and Smith, David C., University of Michigan, Ann Arbor, Michigan; *A Phase I/II Study of a Prime-Boost Schedule of Human GM-CSF Gene Transduced Irradiated Prostate Allogeneic Cancer Vaccine (Allogeneic Prostate GVAX ™) in Hormone-Refractory Prostate Cancer (G9803)* . Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 5-14-99. Not Selected for RAC Public Review: 6-4-99

Notification from sponsor that trial is closed: 4-09-01

9905-316 (Closed) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Percutaneous Cardiac Catheterization

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *Multicenter, Randomized, Single-Blind, Placebo-Controlled, Dose-Escalating Study of Intramyocardial Vascular Endothelial Growth Factor 2 (VEGF2) Gene Therapy Administered Using Percutaneous Cardiac Catheterization in Patients with Refractory and Stable Exertional Angina Who Are Not Candidates for Revascularization Procedures.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 5-21-99. Not Selected for RAC Public Review: 8-30-99
Follow-up is complete: 11-29-01

9905-317 (Open) Gene Therapy/Phase I/Monogenic Disease/Muscular Dystrophy/In Vivo/Adeno-Associated Virus/ α, β, γ, Δ-Sarcoglycan cDNA/Intramuscular Injection

Mendell, Jerry, Ohio State University, Columbus, Ohio; *Phase I Clinical Trial Utilizing Gene Therapy for Limb Girdle Muscular Dystrophy: α, β, γ or Δ-Sarcoglycan Gene Delivered with Intramuscular Instillations of Adeno-Associated Vectors.*

NIH/ORDA Receipt Date: 5-26-99. Publicly Reviewed at the September 2, 1999 RAC meeting

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9905-318 (Closed) Gene Therapy/Phase II/Cancer/Colon/Hepatic Metastasis/Tumor Suppressor Gene/n Vivo/Adenovirus/Serotype 5/p53 cDNA/Intrahepatic/Hepatic Artery/Bolus Infusion

Venook, Alan P. and Warren, Robert S. Warren, University of California, San Francisco, San Francisco, California; Lenz, Heinz-Josef, University of Southern California, Los Angeles, California; Ravikumar, Thanjavur S., Montefiore Medical Center, Bronx, New York; Kardinal, Carl, Alton Ochsner Medical Foundation, New Orleans, Louisiana; Roh, Mark S., Allegheny General Hospital, Pittsburgh, Pennsylvania; Kemeny, Margaret, Stony Brook University Hospital, Stony Brook, New York; Gold, Philip J., University of Washington, Seattle, Washington; Staley III, Charles, Emory University School of Medicine, Atlanta, Georgia; McMasters, Kelly M., University of Louisville, Louisville, Kentucky; Elias, Laurence, University of New Mexico School of Medicine, Albuquerque, New Mexico; and Amado, Rafael G., University of California, Los Angeles, Los Angeles, California; *A Phase II Study of SCH 58500 in Combination with Chemotherapy Alone in Patients with Colorectal Cancer Metastatic to the Liver.* Sponsor: Schering Corporation.

NIH/ORDA Receipt Date: 5-26-99. Not Selected for RAC Public Review: 6-16-99

Notification from sponsor that study is closed to new enrollment at all sites: 3-29-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9905-319 (Open) Gene Therapy/Phase I/Cancer/Acute Leukemia/Immunotherapy/In Vitro/Autologous Bone Marrow Fibroblasts/Lethally Irradiated/Adenovirus/Serotype 5/Interleukin-2 cDNA/CD40 Ligand cDNA/subcutaneous Injection

Brenner, Malcolm, Baylor College of Medicine, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas; *Treatment of High Risk Acute Leukemia with CD40 Ligand and IL-2 Gene Modified Autologous Bone Marrow Fibroblasts and Tumor Cells.*

NIH/ORDA Receipt Date: 5-26-99. Not Selected for RAC Public Review: 6-16-99

9905-320 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Carcinoembryonic Antigen/Intravenous

Lyerly, H. Kim, Duke University Medical Center, Durham, North Carolina; *Pilot Study of CEA RNA-Loaded, FLT3 Ligand-Mobilized Peripheral Blood Antigen Presenting Cells for Patients with Metastatic Malignancies Expressing CEA.*

NIH/ORDA Receipt Date: 5-26-99. Not Selected for RAC Public Review: 9-23-99

9906-321 (Completed) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/Replication-Competent Virus/Pro-Drug/In Vivo/Adenovirus/E. coli Cytosine Deaminase cDNA/5-Fluorocytosine/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Kim, Jae Ho, Henry Ford Health System, Detroit, Michigan; *A Phase I Study of E1B-Attenuated Replication Competent Adenovirus Vector-Mediated Intratumoral Administration of the E. coli Cytosine Deaminase/HSV-1 Thymidine Kinase Fusion Gene in Conjunction with Two Prodrugs, 5-Fluorocytosine and Ganciclovir for Patients with Local Recurrence of Prostate Cancer after Radiation Therapy.*

NIH/ORDA Receipt Date: 6-9-99. Not Selected for RAC Public Review: 6-29-99

Study is completed: 7-3-02

9906-322 (Closed) Gene Therapy/Phase I/Alzheimer's Disease/In Vitro/Autologous Fibroblasts/Retrovirus/Nerve Growth Factor cDNA/Intracerebral Implantation

Tuszynski, Mark H., University of California, San Diego, La Jolla, California; *A Phase I Study of NGF Ex Vivo Gene Therapy for Alzheimer's Disease*

NIH/ORDA Receipt Date: 6-15-99. Publicly Reviewed at the December 1999 RAC meeting.

Closed to enrollment: 6-18-02

9906-323 (Open) Gene Therapy/Phase II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Cationic Liposome Complex/DOTMA-Cholesterol/Interleukin-2 cDNA/Intratumoral Injection

Zarrabi, M. H., Veterans Affairs Medical Center, Northport, New York; Biel, Merrill A., Ear, Nose & Throat SpecialtyCare of Minnesota, P.A., Minneapolis, Minnesota; Krasnow, Steven, Veterans Affairs Medical Center, Washington, D.C.; Cornett, Patricia, University of California, San Francisco/Veterans Affairs Medical Center, San Francisco, California; Robbins, K. Thomas, University of Tennessee, Memphis, Tennessee; O'Malley, Bert W., University of Maryland School of Medicine, Baltimore, Maryland; Kabbinavar, Fairooz, University of California, Los Angeles, Los Angeles, California; McCaffery, Thomas, University of South Florida, Tampa, Florida; and Cordero, Joehassin, Texas Tech University, Lubbock, Texas; *A Multi-Center, Open-Label, Study of the Safety and Efficacy of Multiple Intratumoral Injections of hIl-2 Plasmid (1.8 mg) Formulated with DOTMA/Cholesterol [Ratio 1:0.5 (-/+)] Liposomes in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck.* Sponsor: Valentis, Inc.

NIH/ORDA Receipt Date: 6-17-99. Not Selected for RAC Public Review: 7-8-99

9906-324 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Pro-Drug/Valacyclovir/In Vivo/Adenovirus/Herpes Simplex Thymidine Kinase cDNA/Intratumoral Injection

Butler, E. Brian and Aguilar-Cordova, Estuardo, Baylor College of Medicine, Houston, Texas; *Phase I-II Study Evaluating HSV-tk + Valacyclovir Gene Therapy in Combination with Radiotherapy for Prostate Cancer.*

NIH/ORDA Receipt Date: 6-22-99. Not Selected for RAC Public Review: 7-13-99

9906-325 (Open) Gene Therapy/Phase I/Cancer/Malignant Glioma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Human Interferon-Beta cDNA/Stereotactic Injection

Eck, Stephen L., University of Pennsylvania, Philadelphia, Pennsylvania; *Treatment of Recurrent or Progressive Malignant Glioma with a Recombinant Adenovirus Expressing Human Interferon-Beta (H5.010CMVhIFN-β): A Phase I Trial.*

NIH/ORDA Receipt Date: 6-30-99. Not Selected for RAC Public Review: 7-21-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9906-326 (Open) Gene Therapy/Phase I/Cancer/Skin Metastasis/Immunotherapy/In Vivo/Plasmid DNA/Interleukin-12 cDNA/Intratumoral Injection

Mahvi, David M., University of Wisconsin, Madison, Wisconsin; *Treatment of Spontaneous Tumor Metastases with IL-12 DNA: A Phase IB Trial.*

NIH/ORDA Receipt Date: 6-30-99. Not Selected for RAC Public Review: 7-21-99

9907-327 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Muscle Cells/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Intramuscular Injection

Losordo, Douglas W., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; Chronos, Nicholas, Atlanta Cardiology Group, Saint Joseph's Hospital, Atlanta, Georgia; Deitcher, Steven, Cleveland Clinic Foundation, Cleveland, Ohio; Rajagopalan, Sanjay, University of Michigan; and Laird, John, Washington Hospital Center, Washington, DC; *A Phase I Double-Blind, Placebo Controlled, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization.* Sponsor: Genzyme Corporation.

NIH/ORDA Receipt Date: 7-6-99. Not Selected for RAC Public Review: 10-5-99

9907-328 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Muscle Cells/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Intramuscular Injection

Losordo, Douglas W., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; Chronos, Nicholas, Atlanta Cardiology Group, Saint Joseph's Hospital, Atlanta, Georgia; Deitcher, Steven, Cleveland Clinic Foundation, Cleveland, Ohio; Rajagopalan, Sanjay, University of Michigan; and Laird, John, Washington Hospital Center, Washington, DC; *A Phase I, Open-Label, Multi-Center Extension Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization.* Sponsor: Genzyme Corporation.

NIH/ORDA Receipt Date: 7-6-99. Not Selected for RAC Public Review: 10-5-99

9907-329 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Muscle Cells/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Intramuscular Injection

Losordo, Douglas W., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; Chronos, Nicholas, Atlanta Cardiology Group, Saint Joseph's Hospital, Atlanta, Georgia; Deitcher, Steven, Cleveland Clinic Foundation, Cleveland, Ohio; Rajagopalan, Sanjay, University of Michigan; and Laird, John, Washington Hospital Center, Washington, DC; *A Phase I, Open-Label, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization.* Sponsor: Genzyme Corporation.

NIH/ORDA Receipt Date: 7-6-99. Not Selected for RAC Public Review: 10-5-99

9907-330 (Closed) Gene Therapy/Phase I/Cancer/CD20+ Lymphoma/In Vitro/Autologous T Lymphocytes/Plasmid DNA/Electroporation/CD20-Specific scFvFc-Zeta T Cell Receptor/Intravenous Infusion

Jensen, Michael, City of Hope National Medical Center, Duarte, California; *Pilot Phase I Study to Evaluate the Safety of Cellular Immunotherapy Using Genetically Modified Autologous CD20-Specific CD8+ T Cell Clones for Patients with Recurrent/Refractory CD20+ Lymphoma Undergoing Autologous Peripheral Blood Stem Cell Transplantation.*

NIH/ORDA Receipt Date: 7-8-99. Not Selected for RAC Public Review: 7-28-99

9907-331 (Withdrawn-replaced by protocol # 0004-393) Gene Therapy/Phase II/Cancer/Non-Small Cell Lung Cancer/Antisense/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Plasmid DNA/Electroporation/TGF-β/Subcutaneous Injection

Gutheil, John C. and Fakhrai, Habib, Sharp HealthCare, Sidney Kimmel Cancer Center, San Diego, California; *Phase II Study of Antisense TGF-β +/- IL-2 Gene Transfected Allogeneic Tumor Cells as a Vaccine in Patients with Stage IIIB and IV Non-Small Cell Lung Cancer.* Sponsor: NovaRx Corporation.

NIH/ORDA Receipt Date: 7-8-99.

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9907-332 (Open) Gene Therapy/Phase I-II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Interleukin-12 cDNA/Intratumoral Injection

Colevas, Alexander Dimitrios, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; *A Multi-Center, Open-Label, Multiple Administration, Rising Dose Study of the Safety, Tolerability, and Efficacy of IL-12 Gene Medicine in Patients with Unresectable or Recurrent/Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Valentis, Inc.

NIH/ORDA Receipt Date: 7-16-99. Not Selected for RAC Public Review: 8-5-99

9908-333 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD34+ Hematopoietic Stem Cells/Retrovirus/Transdominant Rev/Antisense Pol 1/Intravenous Infusion

Swindells, Susan, University of Nebraska Medical Center, Omaha, Nebraska; Scadden, David, Massachusetts General Hospital, Boston, Massachusetts; Holodniy, Mark, Veterans Affairs Palo Alto Health Care System, Palo Alto, California; and MacGregor, Rob Roy, University of Pennsylvania Hospitals, Philadelphia, Pennsylvania; *A Multicenter Evaluation of the Safety and Efficacy of Hematopoietic Stem Cells Transduced with RevM10polAS (RevM10polAS HSCIP) as Therapy for HIV-1 Infected Persons.* Sponsor: Systemix, Inc.

NIH/ORDA Receipt Date: 8-16-99. Not Selected for RAC Public Review: 9-3-99

9908-334 (Under Review) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine cDNA/Ganciclovir/Intraperitoneal Injection

Alvarez, Ronald D., Barnes, Mack N., and Curiel, David T. , University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Study of FGF2-Fab' Modified Adenovirus Vector Mediated Intraperitoneal Delivery of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Gene and Intravenous Ganciclovir in Previously Treated Ovarian and Extraovarian Patients.*

NIH/ORDA Receipt Date: 8-17-99. Review at a RAC meeting pending; investigators have requested postponement of public review.

9908-335 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Ovarian/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) cDNA/Subcutaneous or Intradermal Injection

Dranoff, Glenn, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Study of Vaccination with Lethally Irradiated, Autologous Ovarian Carcinoma Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor*

NIH/ORDA Receipt Date: 8-18-99. Not Selected for RAC Public Review: 9-8-99

9908-336 (Open) Gene Marking/Leukemia/In Vitro/CD 34+ Autologous Cord Blood Cells/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous

Croop, James and Cornetta, Kenneth., Indiana University School of Medicine; *Post-Transplant Infusion of Fibronectin-Assisted, Retroviral-Mediated Gene-Marked and Ex Vivo Expanded CD34+ Placental and Umbilical Cord Blood Cells*

NIH/ORDA Receipt Date: 8-19-99. Not Selected for RAC Public Review: 9-9-99

9908-337 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Monogenic Disease/Severe Combined Immune Deficiency due to adenosine Deaminase Deficiency/In Vitro/Autologous CD34+ Cells from Cord Blood or Bone Marrow/Retrovirus/Adenosine Deaminase cDNA/Intravenous Infusion

Kohn, Donald B., Childrens Hospital Los Angeles, University of Southern California, Los Angeles, California; and Brochstein, Joel, Hackensack University Medical Center, Hackensack, New Jersey; *Transduction of CD34+ Cells from the Umbilical Cord Blood of Infants or the Bone Marrow of Children with Adenosine Deaminase (ADA)-Deficient Severe Combined Immunodeficiency (SCID)*

NIH/ORDA Receipt Date: 8-26-99. Publicly Reviewed at the March 2000 RAC meeting

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9909-338 (Open) Gene Therapy/Phase I/Cancer/Prostate/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p 16 cDNA/Intratumoral Injection

Gingrich, Jeffrey R., University of Tennessee, Memphis, Tennessee; *A Tolerance and Efficacy Study of Neoadjuvant Intraprostatic GTx-001 Followed by Radical Prostatectomy in Patients with Locally Advanced Prostate Cancer.* Sponsor: Genotherapeutics, Inc.

NIH/ORDA Receipt Date: 9-2-99. Not Selected for RAC Public Review: 9-29-99

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9909-339 (Open) Gene Therapy/Phase I-II/Cancer/Ovarian/Tumor Suppressor Gene/In Vivo/Retrovirus/BRCA1 Gene/Intraperitoneal Administration

Holt, Jeffrey T., Vanderbilt University, Nashville, Tennessee, and Tait, David L., East Carolina University, Greenville, North Carolina; *Ovarian Cancer Gene Therapy with BRCA1.*

NIH/ORDA Receipt Date: 9-13-99. Not Selected for RAC Public Review: 10-1-99

9909-340 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD34+ Hematopoietic Stem Cells/Retrovirus/Transdominant Rev/Antisense Pol 1/Intravenous Infusion

Carabasi, Mathew H., University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I/II Study to Evaluate the Safety and Effectiveness of RevM10polAS HSCIP in Late-Stage AIDS Patients Given Intensive Myelosuppressive Conditioning.* Sponsor: Systemix Inc.

NIH/ORDA Receipt Date: 9-17-99. Not Selected for RAC Public Review: 10-7-99

9909-341 (Submission Not Complete) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD34+ Cells/Retrovirus/Antisense TAT/Transdominant Rev cDNA/Intravenous
Tisdale, John, National Institutes of Health, Bethesda, Maryland; *Low Intensity Non-Myeloablative Preparative Conditioning Followed by Transplantation of Genetically Modified HLA-Matched Peripheral Blood Hematopoietic Precursor Cells (PBPC) for Hematologic Malignancies in HIV Positive Adults*

NIH/ORDA Receipt Date: 9-20-99.

9910-342 (Open) Gene Therapy/Phase I/Other/Ulcer/In Vivo/Adenovirus/Serotype 5/Platelet Derived Growth Factor (PDGF) cDNA/Intra-Ulcer Injection

Margolis, David J., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *Phase I Trial tot Evaluate the Safety of H5.020CMVPDGF-B for the Treatment of a Diabetic Insensate Foot Ulcer.* Sponsor: Institute for Human Gene Therapy, University of Pennsylvania

NIH/ORDA Receipt Date: 10-1-99. Publicly Reviewed at the December 1999 RAC meeting.

9910-343 (Open) Gene Therapy/Phase I/Other/Ulcer/In Vivo/Adenovirus/Serotype 5/Platelet Derived Growth Factor (PDGF) cDNA/Intra-Ulcer Injection

Margolis, David J., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *Phase I Trial to Evaluate the Safety of H5.020CMVPDGF-B and Limb Compression Bandage for the Treatment of Venous Leg Ulcer (Trial A).* Sponsor: Institute for Human Gene Therapy, University of Pennsylvania

NIH/ORDA Receipt Date: 10-1-99. Publicly Reviewed at the December 1999 RAC meeting.

9910-344 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Vector-Directed Cell Lysis/In Vivo/Adenovirus Type 5/Replication-Competent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen/Intratumoral Injection

Terris, Martha K., Palo Alto Veterans Administration Medical Center, Stanford University, Palo Alto, California; *A Phase I/II Dose Finding Trial of the Intraprostatic Injection of Calydon CV787, a Prostate-Specific Antigen Cytolytic Adenovirus, in Patients with Locally Recurrent Prostate Cancer Following Definitive Radiotherapy.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 10-13-99. Not Selected for RAC Public Review: 11-2-99

9910-345 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Metastatic Prostate Cancer/Vector-Directed Cell Lysis/In Vivo/Adenovirus Type 5/Replication-Competent Virus/Promoter and Enhancer Elements of the Prostate-Specific Antigen/Intravenous Injection

Wilding, George, University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin; *A Phase I/II Dose Finding Trial of the Intravenous Injection of Calydon CV787, a Prostate-Specific Antigen Cytolytic Adenovirus, in Patients with Hormone Refractory Metastatic Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/ORDA Receipt Date: 10-13-99. Publicly Reviewed at the March 2000 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9910-346 (Open) Gene Therapy/Phase II/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Stewart, Duncan J., St. Michael's Hospital, University of Toronto, Toronto, Canada; Buller, Christopher, University of British Columbia, Vancouver, British Columbia, Canada; Rivard, Alain, University of Montreal, Montreal, Canada; Gregoire, Jean C., Montreal Heart Institute, Montreal, Canada; Page, Pierre, Hopital du Sacre-Coeur de Montreal, Montreal, Canada; Plante, Sylvain, Laval Hospital, Sainte-Foy, Canada; Archer, Stephen L., University of Alberta, Alberta, Canada; Sullivan, John, QEII Health Science Center, Halifax, Canada ; Dangoisse, Vincent, Hopital Royal Victoria Hospital, Montreal, Canada; Ducas, John, University of Manitoba, Manitoba, Canada; Hilton, J. David, Victoria Heart Institute, Victoria, Canada; Cohen, Eric A. and Bhatnagar, Gopal, Sunnybrook & Women's College Health Sciences Centre, Toronto, Canada; Langlois, Yves, Jewish General Hospital, Montreal, Quebec; Curtis, Michael, Foothills Hospital/University of Calgary, Alberta, Canada; Arnold, J. Malcolm O., University of Western Ontario, London, Ontario, Canada; Dib, Nabil, Arizona Heart Institute & Foundation; Rajakumar, A. R. J., Royal University Hospital, Saskatoon, Canada; Frank, Michael, Evanston Northwestern Healthcare, Evanston, Illinois; Lowe, James E., Duke University Medical Center, Durham, North Carolina; and Mendelsohn, Farrell O., Cardiology, P.C., Birmingham, Alabama; *A Phase II, Randomized, Multicenter, 26-Week Study to Assess the Efficacy and Safety of CI-1023 Delivered Through Minimally Invasive Surgery Versus Maximum Medical Treatment in Patients with Severe Angina, Advanced Coronary Artery Disease, and No Options for Revascularization.* Sponsor: GenVec, Inc.

NIH/ORDA Receipt Date: 10-12-99. Not Selected for RAC Public Review: 11-5-99

9910-347 (Withdrawn from RAC Review) Gene Therapy/Phase I/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Rosengart, Todd K., Northwestern Healthcare, Northwestern University, Evanston, Illinois; *Assessment of Direct Administration Via Minimally Invasive Surgery of a Replication Deficient Adenovirus Vector (Ad_{CU}VEGF.1) Containing the VEGF cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease.* Sponsor: R. Crystal, Institute of Genetic Medicine, The New York Presbyterian Hospital-Weill College of Cornell University

NIH/ORDA Receipt Date: 10-14-99. Withdrawn from RAC review: 10-16-00

9910-348 (Withdrawn from RAC Review) Gene Therapy/Phase I/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Crystal, Ronald G., Institute of Genetic Medicine, The New York Presbyterian Hospital-Weill College of Cornell University, New York, New York; *Assessment of Direct Administration Via Minimally Invasive Surgery of a Replication Deficient Adenovirus Vector (Ad_{CU}VEGF.1) Containing the VEGF cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease.*

NIH/ORDA Receipt Date: 10-14-99. Withdrawn from RAC review: 10-16-00

9910-349 (Withdrawn-replaced by protocol # 0010-427) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Sweat Duct Epithelium/Adenovirus/Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intradermal Administration

Crystal, Ronald G., Institute of Genetic Medicine, The New York Presbyterian Hospital-Weill College of Cornell University, New York, New York; *Effect of Ad_{GV}CFTR.10 on the Cystic Fibrosis Phenotype.*

NIH/ORDA Receipt Date: 10-14-99.

9910-350 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Oncogene Regulation/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intraperitoneal Administration

Alberts, David S., Arizona Cancer Center, University of Arizona, Tucson, Arizona; Wolf, Judith K., University of Texas, M.D. Anderson Cancer Center, Houston, Texas; and Muntz, Howard, Virginia Mason Medical Center, Seattle, Washington; *A Phase I Dose Escalation Study of Intraperitoneal E1A-Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer.* Sponsor: Targeted Genetics Corporation

NIH/ORDA Receipt Date: 10-14-99. Not Selected for RAC Public Review: 11-3-99

9910-351 (Open) Gene Therapy/Phase II/Cancer/Angioendothelioma/Immunotherapy/In Vivo/Plasmid DNA/Polyvinlypyrrolidone (PVP)/Human Interferon-α cDNA/Intratumoral Injection

Baker, Laurence H., University of Michigan Medical School, Ann Arbor, Michigan; *An Open-Label, Multiple Administration, Study of the Safety, Tolerability, and Efficacy of IFN-α Gene Medicine in Patients with Malignant Angioendothelioma.* Sponsor: Valentis, Inc.

NIH/ORDA Receipt Date: 10-19-99. Not Selected for RAC Public Review: 11-8-99

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9910-352 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1102/Leuvectin/Interleukin-2 cDNA/Intratumoral Injection

Belldegrun, Arie, University of California, Los Angeles Medical Center, Los Angeles, California; Klein, Eric A., Cleveland Clinic Foundation, Cleveland, Ohio; Corman, John, Virginia Mason Medical Center, Seattle, Washington and Moul, Judd, Walter Reed Army Medical Center, Washington, DC; *Phase I/II Study Evaluating the Safety and Efficacy of Leuvectin Immunotherapy for the Treatment of Locally Recurrent Prostate Cancer Following Radiation Therapy.* Sponsor: Vical Inc.

NIH/ORDA Receipt Date: 10-25-99. Not Selected for RAC Public Review: 11-12-99

9911-353 (Submission Not Complete) Gene Therapy/Phase I-II/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/VEGF2-PAD-CL-009/Vascular Endothelial Growth Factor (VEGF) cDNA/Intramuscular Injection

Annex, Brian H., Durham VA Medical Center, Durham, North Carolina; *An Open Label Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with Critical Limb Ischemia.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 11-5-99.

9911-354 (Closed) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/VEGF2-CAD-CL-005/Vascular Endothelial Growth Factor (VEGF) cDNA/Percutaneous Cardiac Catheterization

Isner, Jeffrey M., St. Elizabeth's Medical Center, Boston, Massachusetts; *A Placebo-Controlled, Dose-Escalating Study of Intramyocardial Vascular Endothelial Growth Factor 2 (VEGF2) Gene Therapy Administered Using Percutaneous Cardiac Catheterization in Patients with Class III or IV Angina.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/ORDA Receipt Date: 11-5-99. Not Selected for RAC Public Review: 1-28-00

Follow-up has been completed: 11-29-01

9911-355 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma Multiforme/Anaplastic Astrocytoma/Immunotherapy/In Vitro/Allogeneic Fibroblasts/Lethally Irradiated/Plasmid DNA-Electroporation/IR850-170/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intradermal Injection

Black, Keith L., Cedars-Sinai Medical Center, Los Angeles, California; *A Phase I, Open Label, Safety Study of Allogeneic Glioblastoma Tumor Cell Lines (IR850) Mixed with Allogeneic Fibroblasts Genetically Modified to Secrete GM-CSF (IR851) in Patients with Glioblastoma Multiforme or Anaplastic Astrocytoma.* Sponsor: The Immune Response Corporation

NIH/ORDA Receipt Date: 11-12-99. Not Selected for RAC Public Review: 2-3-00

9911-356 (Closed) Gene Therapy/Phase I/Cancer/MUC-1 Expressing Tumors/Immunotherapy/In Vivo/Vaccinia Virus/TG4010.01/MUC-1/Interleukin-2/Intramuscular Injection

Figlin, Robert and Belldegrun, Arie, University of California, Los Angeles Medical Center, Los Angeles, California; *Phase I Bridging Trial of TG4010 as Antigen-Specific Immunotherapy in Patients with MUC-1 Positive Advanced Cancer.* Sponsor: Transgene, Inc.

NIH/ORDA Receipt Date: 11-16-99. Not Selected for RAC Public Review: 12-6-99

Completed: 9-11-00

9911-357 (Open) Gene Therapy/Phase I-II/Cancer Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical VCL-1102/Leuvectin/Interleukin-2 cDNA/Intratumoral Injection

Galanis, Evanthia, Mayo Clinic, Rochester, Minnesota; and Hawkins, Michael, Washington Hospital Center, Washington Cancer Institute, Washington, D.C.; *Protocol for Retreatment with Leuvectin Immunotherapy for Cancer.* Sponsor: Vical Inc.

NIH/ORDA Receipt Date: 11-18-99. Not Selected for RAC Public Review: 12-8-99

9911-358 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Liver/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Interleukin-12 cDNA/Intratumoral Injection

Sung, Max W. and Woo, Savio L. C., Mount Sinai School of Medicine, New York, New York; *Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12 cDNA by Intratumoral Injection in Patients with Metastatic Breast Cancer to the Liver.*

NIH/ORDA Receipt Date: 11-22-99. Publicly Reviewed at the March 2000 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9911-359 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Liver/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Interleukin-12 cDNA/Intratumoral Injection

Sung, Max W. and Woo, Savio L. C., Mount Sinai School of Medicine, New York, New York; *Phase I Trial of Adenoviral Vector Delivery of the Human Interleukin-12 cDNA by Intratumoral Injection in Patients with Primary or Metastatic Colorectal Cancer to the Liver.*

NIH/ORDA Receipt Date: 11-22-99. Publicly Reviewed at the March 2000 RAC meeting

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9912-360 (Open) Gene Marking/Cancer/Melanoma/In Vitro/Syngeneic Peripheral Blood Lymphocytes/Retrovirus/Neomycin Phosphotransferase Gene/Intravenous Infusion

Rosenberg, Steven A., National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Metastatic Melanoma Using Cloned Lymphocytes Following the Administration of a Nonmyeloablative But Lymphocyte Depleting Regimen.*

NIH/ORDA Receipt Date: 11-22-99. Not Selected for RAC Public Review: 12-31-99

9912-361 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Cationic Liposome Complex/B7 (CD80), HLA-A1 or A2 cDNAs/Subcutaneous Injection

Podack, Eckhard R., Cassileth, Peter A., Sridhar, Kasi, and Savaraj, Niramol, University of Miami, Miami, Florida; *Elicitation of a Cellular Immune Response in Patients with Non-Small Cell Lung Cancer by Immunogenic Tumor Cell Vaccination - A Phase I Study.*

NIH/ORDA Receipt Date: 12-1-99. Not Selected for RAC Public Review: 12-21-99

9912-362 (Open) Gene Marking/Cancer/Melanoma/In Vitro/Syngeneic Peripheral Blood Lymphocytes/Retrovirus/Neomycin Phosphotransferase Gene/Intravenous Infusion

Rosenberg, Steven A., National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Metastatic Melanoma Using Cloned Peripheral Blood Lymphocytes Sensitized In Vitro to the gp209-2M Immunodominant Peptide*

NIH/ORDA Receipt Date: 12-16-99. Not Selected for RAC Public Review: 1-7-00

9912-363 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Penile Carcinoma/Vector-Directed Cell Lysis/Replication-Competent Virus/Pro-Drug/In Vivo/adenovirus/Serotype 5/E. coli Cytosine deaminase Gene/Herpes Simplex Thymidine Kinase cDNA/Valacyclovir/Intratumoral Injection

Miles, Brian J., Ayala, Gustavo, and Aguilar-Cordova, Estuardo, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas; *Phase I Study of the Replication-Competent, E1B-Attenuated Adenovirus with a CD/HSV-1 TK Fusion Gene and the Oral Administration of Valacyclovir in Adults with Penile Cancer.*

NIH/ORDA Receipt Date: 12-20-99. Publicly Reviewed at the March 2000 RAC meeting

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9911-364 (Open) Gene Therapy/Phase I-II/Infectious Disease/Epstein-Barr Virus (EBV) and Cytomegalovirus Diseases/In Vitro/EBV and CMV-Specific Cytotoxic T Lymphocytes/Retrovirus/Cytomegalovirus pp65 Gene/Intravenous

Lucas, Kenneth G., University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I-II Trial to Examine the Toxicity of CMV and EBV Specific Cytotoxic T Lymphocytes When Used for Prophylaxis Against EBV and CMV Disease in Recipients of CD34+ Selected/T Cell Depleted Stem Cell Transplants.*

NIH/ORDA Receipt Date: 11-26-99. Not Selected for RAC Public Review: 1-3-00

9912-365 (Open) Gene Therapy/Phase I-II/Infectious Disease/Human Immunodeficiency Virus/In Vitro/Autologous CD4+ T Cells/Retrovirus/CD4-Zeta Chimeric Receptor/Intravenous Infusion

Aronson, Naomi, Walter Reed Army Medical Center, Washington, D.C.; *A Phase I/II Study of the Safety, Survival, and Trafficking of Autologous CD4-zeta Gene-Modified T Cells With and Without Exogenous Interleukin-2 in HIV-Infected Patients.* Sponsors: University of Pennsylvania and Cell Genesys, Inc.

NIH/ORDA Receipt Date: 12-22-99. Not Selected for RAC Public Review: 4-14-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

9912-366 (Open)Gene Therapy/Phase III/Cancer/Squamous Cell Carcinoma of the Head and Neck (SCCHN)/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5 p53 cDNA/Intratumoral Injections

Hamm, John T., University of Louisville, Norton Healthcare, Louisville, Kentucky; Haigentz, Missak, Montefiore Medical Center, Bronx, New York; Arquette, Mathew, Washington University School of Medicine, Barnard Cancer Center, St. Louis, Missouri; Cullen, Kevin J., Georgetown University Medical Center, Washington, D.C.; Goodwin, W. Jarrard, University of Miami, Miami, Florida; Flood, William A., The Milton S. Hershey Medical Center, Hershey, Pennsylvania; Yoo, George University Health Center, Detroit, Michigan; and Krempl, Greg, The University of Oklahoma, Oklahoma City, Oklahoma; Turpeenniemi-Hujanen, Taina, OULU University Hospital, Oulu, Finland; Kellokumpu-Lehtinen, Pirkko, Tampere University Hospital, Tampere, Finland; Brockstein, Bruce, Evanston Northwestern Healthcare, Evanston, Illinois; Cobb, Patrick, Billings Oncology Associates, Billings, Montana; Williamson, Stephen, University of Kansas Medical Center, Kansas City, Kansas; Burkey, Brian, The Vanderbilt Clinic/Vanderbilt University Medical Center, Nashville, Tennessee; Carrato Mena, Alfredo, Hospital General De Elche, Elche (Spain); Barnadas, Agusti, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; Trigo, J. Ma., Hospital General Vall d'Hebron, Barcelona, Spain; Cortes-Funes, Hernan, Hospital 12 de Octubre, Madrid, Spain; Constenla, Manuel, Complejo Hospitalario De Pontevedra, Pontevedra, Spain; Sanchez, Emilio Fonseca, Hospital Clinico de Salamanca, Salamanca, Spain; Ruiperez, Andres Cervantes, Hospital Clinico Universitaro, Valencia, Spain; Guillem, Vicente, Instituto Valenciano de Oncologia, Valencia, Spain; Nathan, Cherie-Ann, Louisiana State University, Shreveport, Louisiana; Agarwala, Sanjiv, University of Pittsburgh, Pittsburgh, Pennsylvania; Rosen, Fred, The University of Illinois at Chicago, Chicago, Illinois; Breau, Randall, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Giguere, Jeffrey, Cancer Center of the Carolinas, Greenville, South Carolina; Trask, Douglas, University of Iowa Hospitals and Clinics, Iowa City, Iowa; Zitsch, Robert, University of Missouri Health Care, Columbia, Missouri; Hrushesky, William, J. M., Dorn Veterans Affairs Medical Center, Columbia, South Carolina; Clayman, Gary, University of Texas, MD Anderson Cancer Center, Houston, Texas; Guthrie, Troy H., Jr., University of Florida, Jacksonville, Florida; Slolomon, William, SUNY Health Science Center at Brooklyn, Brooklyn, New York; Law, Amy, Geisinger Medical Center, Danville, Pennsylvania; Trask, Douglas, University of Iowa Health Care, Iowa City, Iowa; Nemechek, Andrew, Tulane University School of Medicine, New Orleans, Louisiana; Villaret, Douglas, University of Florida, Gainesville, Florida; Van Echo, David, University of Maryland School of Medicine, Baltimore, Maryland; McCaffrey, Thomas V., H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; Wheeler, Richard H., Huntsman Cancer Institute, Salt Lake City, Utah; Chen, Amy, Emory University, Atlanta, Georgia; and Gal, Thomas, Jr., University of Washington Medical Center, Seattle, Washington; *A Phase III Multi-Center, Open-Label, Randomized Study to Compare the Overall Survival and Safety of Bi-Weekly Intratumoral Administration of INGN 201 Versus Weekly Methotrexate in 240 Patients with Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Aventis Pharmaceuticals - Gencell Division (formerly Rhone-Poulenc Rorer)

NIH/ORDA Receipt Date: 12-28-99. Publicly Reviewed at the March 2000 RAC meeting

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9912-367 (Open) Gene Therapy/Phase I/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Total Tumor RNA/Intravenous

Vieweg, Johannes, Duke University Medical Center, Durham, North Carolina; *Active Immunotherapy of Metastatic Renal Cell Carcinoma Using Autologous Dendritic Cells Transfected with Autologous Renal Tumor RNA.*

NIH/ORDA Receipt Date: 12-28-99. Not Selected for RAC Public Review: 1-14-00

9912-368 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen/B7.1 (CD80)/Intramuscular or Intradermal Injection

Dahut, Bill, National Naval Medical Center, Bethesda, Maryland; and Gulley, James, National Institutes of Health, Bethesda, Maryland; *A Randomized Phase II Study of a PSA-Based Vaccine in Patients with Localized Prostate Cancer Receiving Standard Radiotherapy.*

NIH/ORDA Receipt Date: 12-29-99. Not Selected for RAC Public Review: 3-7-00

0001-369 (Open) Gene Therapy/Phase I/Immunotherapy/Cancer/Myelodysplasia or Acute Myelogenous Leukemia (AML)/In Vitro/Autologous Acute Myeloblastic Leukemia Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) cDNA/Subcutaneous or Intradermal Injection

DeAngelo, Daniel J., Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Study of Vaccination with Lethally Irradiated, Autologous Acute Myeloblastic Leukemia Cells Engineered by Adenoviral Mediated Gene Transfer to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor in Patients with Advanced Myelodysplasia or Acute Myelogenous Leukemia.*

NIH/OBA Receipt Date: 1-3-00. Not Selected for RAC Public Review: 1-24-00

0001-370 (Open) Gene Therapy/Phase I/Monogenic Disease/Fanconi Anemia/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Fanconi Anemia Complementation Group A and C cDNA/Intravenous

Croop, James M., Indiana University School of Medicine, Indianapolis, Indiana; *Gene Therapy for Patients with Fanconi Anemia: A Pilot Study.*

NIH/OBA Receipt Date: 1-6-00. Not Selected for RAC Public Review: 2-4-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0001-371 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Monogenic Disease/Hemophilia B/In Vivo/Adeno-Associated Virus/Factor IX Gene/Intrahepatic Artery Administration

Glader, Bertil, Stanford University, Stanford, California; and Manno, Catherine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; *A Phase I Safety Study in Patients with Severe Hemophilia B (Factor IX Deficiency) Using Adeno-Associated Viral Vector to Deliver the Gene for Human Factor IX into the Liver.*

NIH/OBA Receipt Date: 1-7-00. Publicly Reviewed at the March 2000 RAC meeting

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0001-372 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Monogenic Disease/Hemophilia A/In Vivo/Helper-Dependent (Gutted) Adenovirus/Factor VIII cDNA/Intravenous Injection

White II, Gilbert, University of North Carolina School of Medicine, Chapel Hill, North Carolina; Thompson, Arthur, University of Washington, Seattle, Washington; and Gruppo, Ralph A., Children's Hospital Medical Center, Cincinnati, Ohio; *A Phase 1, Single-Dose, Dose-Escalation Study of MiniAdFVIII Vector in Patients with Severe Hemophilia A.* Sponsor: Corautus Genetics, Inc. (formerly GenStar Therapeutics Corporation)

NIH/OBA Receipt Date: 1-12-00. Publicly Reviewed at the September 2000 RAC meeting

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0001-373 (Open) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen/B7.1 (CD80)/Intramuscular or Intradermal Injection
Arlen, Philip M., National Naval Medical Center and National Institutes of Health, Bethesda, Maryland; *A Randomized Phase II Study of Either Immunotherapy with a Regimen of Recombinant Pox Viruses that Express PSA/B7.1 Plus Adjuvant GM-CSF and IL-2 or Hormone Therapy with Nilutamide in Patients with Hormone Refractory Prostate Cancer and No Radiographic Evidence of Disease.*

NIH/OBA Receipt Date: 1-10-00. Not Selected for RAC Public Review: 3-7-00

0001-374 (Withdrawn-replaced by 0007-407) Gene Therapy/Phase I/Coronary Artery Disease/In Vivo/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Cardiac Administration

A Phase I Open Label, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention and the related follow-up study *A Phase I Open Label, Multi-Center Extension Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administered by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention.* Sponsor: Genzyme Corporation.

NIH/OBA Receipt Date: 1-13-00.

0001-375 (Withdrawn-replaced by protocol # 0010-425) Gene Therapy/Phase I/Other Disorders/Hip Fracture/In Vivo/Plasmid DNA/Collagen Sponge/Parathyroid Hormone cDNA/Bone Administration

A Phase I Safety, Tolerance and Pharmacokinetic Study of Mat-100 in Elderly Patients with Fresh Fracture of the Hip. Sponsor: Selective Genetics, Inc.

NIH/OBA Receipt Date: 1-13-00.

0001-376 (Open) Gene Therapy/Phase I/Cancer/Non-Hodgkin's Lymphoma/Chemoprotection/Fusion Gene of a Mutant Dihydrofolate Reductase and Cytidine Deaminase/In Vitro/Autologous Peripheral Blood CD34+ Cells/Retrovirus/Intravenous Infusion

Bertino, Joseph, Memorial Sloan Kettering Cancer Center, New York, New York; *A Gene Therapy Based Myeloprotection Strategy Using a Mutant Dihydrofolate Reductase - Cytidine Deaminase Fusion Gene for the Treatment of Refractory or Relapsed Non-Hodgkin's Lymphoma.*

NIH/OBA Receipt Date: 1-13-00. Not Selected for RAC Public Review: 2-3-00

0001-377 (Withdrawn from RAC Review) Gene Therapy/Phase I/Monogenic Disease/Fabry Disease/In Vitro/Autologous Mesenchymal Stem Cells/Retrovirus/α-Galactosidase A cDNA/Immunoisolation Device/Subcutaneous Implantation

Medin, Jeffrey A., University of Illinois at Chicago, Chicago, Illinois; *A Phase I Trial of Retroviral Transduction of Autologous Mesenchymal Stem Cells from Patients with Fabry Disease with Alpha-Galactosidase A cDNA and Implantation Via an Immunoisolation Device.* Sponsor: Osiris Therapeutics, Inc.

NIH/OBA Receipt Date: 1-13-00. Withdrawn from RAC review: 3-1-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0002-378 (Open) Gene Therapy/Phase II/Cancer/Squamous Cell Carcinoma of the Head and Neck/Immunotherapy/In Vivo/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Interferon-α/Interleukin-12 cDNA/Intratumoral Injection

McQuone, Shelly J., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *A Multicenter, Open-Label, Multiple Administration, Study of the Safety, Tolerability and Efficacy of IFNα/IL-12 Combination Gene Therapy in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 2-9-00. Not Selected for RAC Public Review: 8-8-00

0001-379 (Submission Not Complete) Gene Therapy/Phase I/Immunotherapy/Cancer/Colon/Adenovirus/Serotype 5/GA733-2 Antigen cDNA/Intradermal Injection

Eck, Stephen L., University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *Phase I Trial of Intradermal Adenovirus GA733 Vaccine for Advanced Colorectal Cancer.*

NIH/OBA Receipt Date: 1-13-00.

0001-380 (Under Review) Gene Therapy/Phase I/Monogenic Disease/Amyotrophic Lateral Sclerosis/In Vivo/Adeno-Associated Virus/Excitatory Amino Acid Transporter 2 (EAAT2) cDNA/Percutaneous Cervical Injection

During, Matthew J. and Simeone, Frederick A., Thomas Jefferson University, Philadelphia, Pennsylvania; *Clinical Trial in Amyotrophic Lateral Sclerosis Patients Using Gene Transfer of the EAAT2 Gene in the Cervical Spinal Cord.*

NIH/OBA Receipt Date: 1-13-00. Review at a RAC meeting pending; investigators have requested postponement of public review.

0001-381 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Monogenic Disease/Canavan Disease/In Vivo/Adeno-Associated Virus/Aspartoacylase cDNA/Stereotactic Intracranial Administration

Leone, Paola and Feely, Michael, Cooper Health System, Camden, New Jersey; *Gene Therapy of Canavan Disease using AAV for Brain Gene Transfer.*

NIH/OBA Receipt Date: 1-13-00. Publicly Reviewed at the March 2000 RAC meeting

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0001-382 Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Autologous Neuroblastoma Cells/Lethally Irradiated/Adenovirus/Serotype 5/Interleukin-2 cDNA/Subcutaneous Injection

Russell, Heidi, Baylor College of Medicine, Houston, Texas; *A Pilot Study of Gene Modified Autologous Neuroblastoma Vaccine for the Post-Chemotherapy Treatment of High Risk Neuroblastoma.*

NIH/OBA Receipt Date: 1-14-00.

0001-383 (Withdrawn) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Catheterization

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Phase IIb Multicenter, Randomized, Controlled Study of Direct Intramyocardial Injection of pVGI.1 (VEGF2) Versus Maximum Medical Therapy in Patients with Class III or IV Angina.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/OBA Receipt Date: 1-18-00.
Withdrawn from consideration, no individuals enrolled: 11-29-01

0001-384 (Withdrawn) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Cardiac Catheterization

Isner, Jeffrey M., Tufts University School of Medicine and St. Elizabeth's Medical Center, Boston, Massachusetts; *A Double-Blind, Placebo-Controlled, Continuation Study of Intramyocardial pVGI.1 (VEGF2) Administered by Percutaneous Cardiac Catheterization in Patients with Class III or IV Angina.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/OBA Receipt Date: 1-18-00.
Withdrawn from consideration, no individuals enrolled: 11-29-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0001-385 (Open) Gene Therapy/Phase I-II/Immunotherapy/Cancer/Non-Small Cell Lung Carcinoma (NSCLC)/In Vitro/Autologous Tumor Cells/Lethally Irradiated/Adenovirus/Serotype 5/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)/Subcutaneous Injection

Smith II, John W., Providence Portland Medical Center, Portland, Oregon; Jablons, David, University of California, San Francisco, San Francisco, California; and Sterman, Daniel, University of Pennsylvania, Philadelphia, Pennsylvania; *Phase I/II Study of GM-CSF Gene-Modified Autologous Tumor Vaccines in Early and Advanced Stage Non-Small Cell Lung Cancer (NSCLC).* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 1-20-00. Not Selected for RAC Public Review: 2-9-00

0001-386 (Open) Gene Therapy/Phase II/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vitro/Autologous Tumor Cells/Irradiated/Canarypox Virus/B7.1 (CD80) cDNA/Subcutaneous Injection

Antonia, Scott J., H. Lee Moffitt Cancer Center, University of South Florida, Tampa, Florida; *Phase II Study of a B-7.1 Gene Modified Autologous Tumor Cell Vaccine and Systemic IL-2 for Patients with Stage IV Renal Cell Carcinoma.*

NIH/OBA Receipt Date: 1-24-00. Not Selected for RAC Public Review: 2-29-00

0001-387 (Open) Gene Therapy/Phase II/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Kornowski, Ran, Cardiovascular Research Institute, Washington, D.C.; Dib, Nabil, Arizona Heart Institute & Foundation, Phoenix, Arizona; Cohen, Barry M., Morristown Memorial Hospital, Morristown, New Jersey; and Moses, Jeffrey W., Lenox Hill Heart Hospital, New York, New York; *A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 12-Week Follow-up, Pilot Study of the Tolerability and Feasibility of Administering $AD_{GV}VEGF_{121.10}$ (CI-1023) Via the Biosense Intramyocardial Injection Device to Patients with Advanced Coronary Artery Disease.* Sponsor: GenVec, Inc.

NIH/OBA Receipt Date: 1-27-00. Not Selected for RAC Public Review: 2-24-00

0002-388 (Open) Gene Therapy/Phase II/Other/Peripheral Arterial Disease/In Vivo/Ischemic Lower Limb/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Intramuscular Injection

Rajagopalan, Sanjay, University of Michigan Medical Center, Ann Arbor, Michigan; Chaikof, Elliot, Emory University School of Medicine, Atlanta, Georgia; Deitcher, Steven, The Cleveland Clinic Foundation, Cleveland, Ohio; Rhee, Robert Y., University of Pittsburgh, Pittsburgh, Pennsylvania; Corson, John D., The University of Iowa Hospitals and Clinics, Iowa City, Iowa; Mohler, Emile R., University of Pennsylvania Health System, Philadelphia, Pennsylvania; Jaff, Michael, Cardiovascular Research Institute, Washington, DC; Goldman, Corey K., Watson Clinic Center for Research, Lakeland, Florida; Blebea, John, Penn State College of Medicine, Hershey, Pennsylvania; Hirsch, Alan T., University of Minnesota, Minneapolis, Minnesota; Annex, Brian H., Duke University Medical Center, Durham, North Carolina; Guzman, Raul, Vanderbilt University Medical Center, Nashville, Tennessee; Tenaglia, Alan, Tulane University Health Sciences Center, New Orleans, Louisiana; Azrin, Michael, University of Connecticut Health Center, Farmington, Connecticut; Gagne, Paul, New York University School of Medicine, New York, New York; Dib, Nabil, Arizona Heart Institute & Foundation, Phoenix, Arizona; Garza, Luis, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Hermiller, James, The Care Group, Indianapolis, Indiana; Mendelsohn, Farrell, Baptist Health System, Birmingham, Alabama; Miller, Julie M., Johns Hopkins University, Baltimore, Maryland; Anderson, R. David, Sarasota Memorial Healthcare System, Sarasota, Florida; and Davies, Mark G., University of Rochester Medical Center, Rochester, New York; *A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 ($AD_{GV}VEGF_{121.10}$) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication.* Sponsor: GenVec, Inc.

NIH/OBA Receipt Date: 2-2-00. Not Selected for RAC Public Review: 3-27-00

0002-389 (Open) Gene Therapy/Phase I/Cancer/Liver Metastasis of Colorectal Carcinoma/Immunotherapy/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Interleukin-2 cDNA/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Sung, Max W., Mount Sinai School of Medicine, New York, New York; *Phase I/IB Trial of Combination Adenoviral Vector Delivery of the Human Recombinant Interleukin-2 Gene and the Herpes Simplex Virus Thymidine Kinase Gene by Intratumoral Injection and Followed by Intravenous Ganciclovir in Patients with Hepatic Metastases from Colorectal Cancer.*

NIH/OBA Receipt Date: 2-4-00. Not Selected for RAC Public Review: 3-10-00

0003-390 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/In Vitro/CD 34+ Hematopoietic Stem Cells/Retrovirus/Transdominant Rev/Intravenous Infusion

Kohn, Donald B., Childrens Hospital Los Angeles, University of Southern California, Los Angeles, California; *Retroviral-Mediated Transfer of the RevM10 and FX Genes into CD 34+ Cells from the Bone Marrow of HIV-1 Infected Children.*

NIH/OBA Receipt Date: 3-1-00. Not Selected for RAC Public Review: 3-21-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0002-391 (Closed) Gene Therapy/Phase II/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE/Vical-1102/Leuvectin/Interleukin-2 cDNA/Intratumoral Injection/Vical Protocol VCL-1102-204

Thompson, John A., University of Washington School of Medicine, Seattle, Washington; Hawkins, Michael, Washington Hospital Center, Washington Cancer Institute, Washington, D.C.; Figlin, Robert A., University of California Los Angeles Medical Center, Los Angeles, California; Lee, Fa-Chyi, University of New Mexico Cancer Research and Treatment Center and University Hospital, Albuquerque, New Mexico; Ernstoff, Marc S., Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; Bukowski, Ronald, The Cleveland Clinic Foundation, Cleveland, Ohio; Morse, Michael A., Duke University Medical Center, Durham, North Carolina; and Amato, Robert, Baylor College of Medicine, Houston, Texas; *Phase II Study of Leuvectin in Patients with Metastatic Renal Cell Carcinoma.* Sponsor: Vical Inc.

NIH/OBA Receipt Date: 2-14-00. Not Selected for RAC Public Review: 3-6-00

Notification from sponsor that study is closed: 6-29-01.

0003-392 (Closed) Gene Therapy/Phase I-II/Cancer/Non-Hodgkin's B-Cell Lymphoma/Mantle Cell Lymphoma/Immunotherapy/In Vivo/Naked Plasmid DNA/Tumor Idiotype/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intramuscular and Intradermal Injections/Vical Protocol VCL-1642-101

Levy, Ronald, Stanford University School of Medicine, Stanford, California; *Phase I/II Study of Vaccine Therapy for B-Cell Lymphoma Utilizing Plasmid DNA Coding for Tumor Idiotype.* Sponsor: Vical Inc.

NIH/OBA Receipt Date: 3-17-00. Not Selected for RAC Public Review: 4-6-00

0004-393 (Open) Gene Therapy/Phase II/Cancer/Non-Small Cell Lung Cancer/Antisense/In Vitro/Allogeneic Tumor Cells/Irradiated/Plasmid DNA-Electroporation/TGF-β/Subcutaneous Injection

Sobol, Robert and Bodkin, David, Sharp Health Care, Sidney Kimmel Cancer Center, San Diego, California; Batra, Raj K., University of California, Los Angeles and West Los Angeles Veteran's Administration Medical Center, Los Angeles, California; and Dillman, Robert O., Hoag Cancer Center, Newport Beach, California; *Phase II Study of a TGF-β2 Antisense Gene Modified Allogeneic Tumor Cell Vaccine in Patients with Stages II-IV Non-Small Cell Lung Cancer.* Sponsor: NovaRx

NIH/OBA Receipt Date: 4-3-00. Not Selected for RAC Public Review: 5-2-00

0005-394 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Naked Plasmid/Tyrosinase cDNA/Intramuscular Injection

Wolchok, Jedd, Memorial Sloan-Kettering Cancer Center, New York, New York; *Vaccination of AJCC Stage III and IV Melanoma Patients with Human and Mouse Tyrosinase DNA Vaccines: A Phase I Trial to Assess Safety and Immune Response.*

NIH/OBA Receipt Date: 5-1-00. Not Selected for RAC Public Review: 5-19-00

0005-395 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vivo/Adenovirus/Type 5/MART-1 Melanoma Antigen/gp100 Melanoma Antigen/Intradermal Injection

Haluska, Frank G, Harvard Medical School, Boston, Massachusetts; Cunningham, Charles, US Oncology, Dallas, Texas; Ernstoff, Marc, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; and Richards, Jon M., Oncology Specialists, S. C., Chicago, Illinois; *A Phase I/II Trial Investigating the Safety and Immunogenicity of Adenoviruses Encoding the Melan-A/MART-1 and gp100 Melanoma Antigens Administered Intradermally to Patients with Stage II-IV Melanoma.* Sponsor: Genzyme Corporation

NIH/OBA Receipt Date: 5-1-00. Not Selected for RAC Public Review: 9-14-00

0005-396 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Colon Carcinoma (Hepatic Metastasis)/Herpes Simplex Virus Type 1/Tumor Lysis/Intrahepatic Artery Administration

Fong, Yuman, Memorial Sloan Kettering Cancer Center, New York, New York; *A Phase I, Open -Label, Dose-Escalating Study of the Safety, Tolerability, and Anti-tumor Activity of a Single Intrahepatic Injection of a Genetically Engineered Herpes Simplex Virus, NV1020, in Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver* and the associated, long-term follow-up protocol: *Long-Term Follow-Up of the Safety and Survival of subjects with Adenocarcinoma of the Colon with Metastasis to the Liver Who Enrolled in a Phase I Dose-Escalating Study Evaluating a Genetically Engineered Herpes Simplex Virus, NV1020.* Sponsor: NeuroVir Therapeutics, Inc.

NIH/OBA Receipt Date: 5-2-00. Publicly Reviewed at the June 2000 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0005-397 (Open) Gene Therapy/Phase I/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration (Catheter)

Sanborn, Timothy A., Joan and Sanford I. Weill Medical College, Cornell University, New York, New York; *A Feasibility Study of Catheter-Based Administration of a Replication Deficient Adenovirus Vector (Ad_{CU}VEGF.1) to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease.* Sponsor: R. Crystal, M.D.

NIH/OBA Receipt Date: 5-3-00. Not Selected for RAC Public Review: 5-23-00

0005-398 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Ovarian/Pro-Drug/In Vivo/Tropism-Modified Adenovirus/Serotype 5/Herpes Simplex Virus Thymidine Kinase cDNA/Somatostatin Receptor cDNA/Ganciclovir/Intraperitoneal Injection

Barnes, Mack N., University of Alabama at Birmingham, Birmingham, Alabama; *A Phase I Study of a Tropism Modified Adenovirus Vector for Intraperitoneal Delivery of Therapeutic Genes in Ovarian and Extraovarian Cancer Patients.*

NIH/OBA Receipt Date: 5-3-00. Publicly Reviewed at the December 2000 RAC meeting

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0005-399 (Open) Gene Therapy/Phase I/Cancer/Solid Tumors/Immunotherapy/In Vivo/Adenovirus/Type 5/Tumor Necrosis Factor cDNA/Intratumoral Injection

Guha, Chandan and Mani, Sridhar, Albert Einstein College of Medicine, Bronx, New York; Hanna, Nader, University of Kentucky Medical Center, Lexington, Kentucky; Nemunaitis, John, US Oncology, Dallas, Texas; Richards, Donald A., Tyler Cancer Center, Tyler, Texas; and Rosemurgy, Alexander, University of South Florida, Tampa, Florida; *An Open-Label, Phase I, Dose-Escalation Study of Tumor Necrosis Factor-alpha (TNFerade™ Biologic) Gene Therapy with Radiation Therapy for Locally Advanced, Recurrent, or Metastatic Solid Tumors.* Sponsor: GenVec

NIH/OBA Receipt Date: 5-3-00. Not Selected for RAC Public Review: 5-23-00

0005-400 (Open) Gene Therapy/Phase I/Cancer/Lymphoma/Chemoprotection/In Vitro/CD34+ Autologous Peripheral Blood Cells/Retrovirus/Multi-Drug Resistance-1 cDNA/Intravenous Infusion

Becker, Pamela S., University of Massachusetts Memorial Health Care, Worcester, Massachusetts; *Transfer of the Multidrug Resistance Gene, MDR-1, to Hematopoietic Progenitors from Patients with High Risk Lymphoma.*

NIH/OBA Receipt Date: 5-3-00. Not Selected for RAC Public Review: 6-5-00

0005-401 (Open) Gene Therapy/Phase II/Cancer/Chronic Lymphocytic Leukemia/Immunotherapy/In Vitro/Autologous Leukemic Cells/Adenovirus/Serotype 5/CD154 cDNA/Intravenous Infusion

Gribben, John, Dana-Farber Cancer Institute, Boston, Massachusetts; and Saville, M. Wayne, University of California-San Diego Medical Center, San Diego, San Diego, California; *Open-Label, Multicenter, Phase II Study of Autologous Ad-CD154 Expressing Transduced CLL Cells in B Cell Chronic Lymphocytic Leukemia Subjects Enrolled in Two Parallel Arms.* Sponsor: Tragen Pharmaceuticals (formerly Immunogenex, Inc.)

NIH/OBA Receipt Date: 5-3-00. Not Selected for RAC Public Review: 5-23-00

0006-402 (Closed) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Autologous T Lymphocytes/Plasmid DNA/Electroporation/CE7R-Specific scFvFc-Zeta T Cell Receptor/Intravenous Infusion

Jensen, Michael, City of Hope National Medical Center, Duarte, California; *Phase I Study to Evaluate the Safety of Cellular Immunotherapy for Recurrent/Refractory Neuroblastoma Using Genetically-Modified Autologous CD8+ T Cell Clones.*

NIH/OBA Receipt Date: 6-2-00. Not Selected for RAC Public Review: 6-22-00

0006-403 (Open) Gene Therapy/Phase IIb/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Fibroblast Growth Factor (FGF) cDNA/Intracoronary Administration

Iskandrian, Ami E., University of Alabama at Birmingham, Birmingham, Alabama; Churchill, David, North West Arkansas Heart and Vascular Center, Fayetteville, Arkansas; Gammon, Roger S., Austin Heart, P.A., Austin, Texas; Ghali, Jalal K., Cardiac Centers of Louisiana, LLC, Shreveport, Louisiana; Grines, Cindy L., William Beaumont Hospital, Royal Oak, Michigan; Helmer, Gregory A., Minnesota Heart Clinic, P. A., Edina, Minnesota; Kleiman, Neal, S., Baylor College of Medicine, Houston, Texas; Rade, Jeffrey J., The Johns Hopkins Hospital, Baltimore, Maryland; Rowe, Steven K., Heartland Health Center, St. Joseph, Missouri; Watkins, Matthew W., Fletcher Allen Health Care, Burlington, Vermont; and Uretsky, Barry, University of Texas, Galveston, Galveston, Texas; *A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effect of Ad5FGF-4 on Myocardial Perfusion Defect Size and Safety in Patients with Stable Angina.* Sponsor: Berlex Laboratories

NIH/OBA Receipt Date: 6-5-00. Not Selected for RAC Public Review: 8-18-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0006-404 (Closed, RAC Reviewed with Recommendations) Gene Therapy/Phase II/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) cDNA/Aerosol Administration

Moss, Richard B., Stanford University School of Medicine, Palo Alto, California; Waltz, David, Children's Hospital, Boston, Massachusetts; Rodman, David, University of Colorado Health Sciences Center, Denver, Colorado; Spencer, L. Terry, Virella-Lowell, Isabel, Brantly, Mark, and Flotte, Terry, University of Florida, Gainesville, Florida; Zeitlin, Pamela, Johns Hopkins University, Baltimore, Maryland; Aitken, Moira, University of Washington, Seattle, Washington; Milla, Carlos, University of Minnesota, Minneapolis, Minnesota; and Clancy, John Paul, University of Alabama at Birmingham, Birmingham, Alabama; *A Multicenter, Double-Blind, Placebo-Controlled, Phase II Study of Aerosolized AAVCF in Cystic Fibrosis Patients with Mild Lung Disease.* Sponsor: Targeted Genetics

NIH/OBA Receipt Date: 6-12-00. Publicly Reviewed at the September 2000 RAC meeting
Enrollment is complete: 10-3-02

0006-405 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD 80)/ICAM-1/LFA-3/Intramuscular Or Intradermal Injection

Marshall, John L., Georgetown University Medical Center, Washington, D.C.; *A Phase I Study of Sequential Vaccinations with Fowlpox-CEA(6D)-TRICOM (B7.1/ICAM-1/LFA-3) Alone, OR in Combination with Vaccinia-CEA(6D)-TRICOM, and the Role of GM-GSF, in Patients with CEA Expressing Carcinomas.*

NIH/OBA Receipt Date: 6-12-00. Not Selected for RAC Public Review: 11-7-00

0006-406 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Anemia of End Stage Renal Disease (ESRD)/In Vitro/Autologous Vascular Smooth Muscle Cells/Retrovirus/Erythropoietin (EPO) cDNA/Vascular Grafts Lined with Transduced Smooth Muscle Cells

Muczynski, Kimberly A. and Osborne, William R. A., University of Washington School of Medicine, Seattle, Washington; *Erythropoietin Administration in Hemodialysis Patients Using Vascular Grafts Lined with Transduced Smooth Muscle Cells.*

NIH/OBA Receipt Date: 6-13-00. Publicly Reviewed at the September 2000 RAC meeting

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0007-407 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Coronary Artery Disease/In Vivo/Adenovirus/Serotype 2/Hypoxia Inducible Factor (HIF)-1α/VP16 cDNA/Cardiac Administration/CAD-HIF-004-99

Rosengart, Todd K, Northwestern University Medical School, Evanston, Illinois; McCurry, Kenneth, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Cmolik, Brian L., University Hospitals of Cleveland, Cleveland, Ohio; Landolfo, Kevin P., Duke University Medical Center, Durham, North Carolina; Dullum, Mercedes, Washington Hospital Center, Washington, DC; Lattouf, Omar, Emory University School of Medicine, Atlanta, Georgia; Fontana, Gregory, Cedars-Sinai Medical Center, Beverly Hills, California; Chronos, Nicolas, Atlanta Cardiology Research Institute, Atlanta, Georgia; and Henry, Timothy, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; *A Phase I, Double-blind, Placebo Controlled, Escalating Dose, Multi-center Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 Gene Transfer Administration by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention.* Sponsor: Genzyme Corporation

NIH/OBA Receipt Date: 7-31-00. Publicly Reviewed at the September 2000 RAC meeting

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0007-408 (Open) Gene Therapy/Phase I-II/Cancer/B-Cell Chronic Lymphocytic Leukemia/Immunotherapy/In Vivo/Naked Plasmid DNA/Tumor Idiotype/Intramuscular Injection

Garcia-Manero, Guillermo, University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I/II Study of Idiotypic Vaccination for Chronic Lymphocytic Leukemia using a Genetic Approach.*

NIH/OBA Receipt Date: 7-31-00. Not Selected for RAC Public Review: 8-18-00

0007-409 (Open) Gene Therapy/Phase I/Cancer/Lung Cancer/Immunotherapy/In Vivo/Cationic Liposome Complex/Interleukin-2 cDNA/Intravenous Injection

Hainsworth, John Daniel, Sarah Cannon Cancer Center, Centennial Medical Center, Nashville, Tennessee; and Antonia, Scott, H. Lee Moffitt Cancer Center, Tampa, Florida; *A Phase I, Multi-Center, Open-Label, Dose-Escalation Study of the Safety and Tolerability of Intravenously Administered VLTS-587 in Patients with Solid Tumors and the Presence of Metastases or Primary Cancer in the Lungs.* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 7-28-00. Not Selected for RAC Public Review: 9-7-00

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0008-410 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Total Tumor RNA/Intravenous

Vieweg, Johannes, Duke University, Durham, North Carolina; *A Safety and Feasibility Study of Active Immunotherapy in Patients with Metastatic Prostate Carcinoma Using Autologous Dendritic Cells Pulsed with Antigen Encoded in Amplified Autologous Tumor RNA.*

NIH/OBA Receipt Date: 8-22-00. Not Selected for RAC Public Review: 9-12-00

0009-411 (Closed, RAC Reviewed with Recommendations) Gene Therapy/Phase I/Other Disorders/Restenosis/In Vivo/Vascular Smooth Muscle Cells/Cationic Liposome Complex/Inducible Nitric Oxide Synthase (iNOS) cDNA/Barath® Intramural Local Drug Delivery Device (Infiltrator®)

Kuntz, Richard E.; Brigham and Women's Hospital, Boston, Massachusetts; *Restenosis Gene Therapy Trial - Phase I Study (REGENT I).* Sponsor: Cardion AG

NIH/OBA Receipt Date: 9-20-00. Publicly Reviewed at the December 2000 RAC meeting
Closed: 10-01

0009-412 (Open) Gene Therapy/Phase III/Cancer/Squamous Cell Carcinoma of the Head and Neck (SCCHN)/Tumor Suppressor Gene/In Vivo/Adenovirus Serotype 5/p53 cDNA/Intratumoral Injections [INGN 201 (Ad5CMV-p53)-T302]

Haigentz, Missak, Montefiore Medical Center, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York; Nemunaitis, John J., Mary Crowley Medical Research Center, Dallas, Texas; Hamm, John T, Louisville Oncology, Norton Healthcare, Inc., Louisville, Kentucky; Spiro, Jeffrey, University of Connecticut Health Center, Farmington, Connecticut; Van Echo, David, University of Maryland, Baltimore, Maryland; Yoo, George, Wayne State University, Detroit, Michigan; Cobb, Patrick, Billings Oncology Associates, Billings, Montana; Brockstein, Bruce, Evanston Hospital, Evanston, Illinois; Flood, William, The Milton S. Hershey Medical Center, Hershey, Pennsylvania; Krempl, Greg, University Hospital, Oklahoma City, Oklahoma; Goodwin, W. Jarrard, University of Miami Hospital and Clinics, Miami, Florida; Trask, Douglas, University of Iowa Hospitals and Clinics, Iowa City, Iowa; Zitsch, Robert, University of Missouri Health Care, Columbia, Missouri; Breau, Randall, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Cullen, Kevin, Georgetown University Medical Center, Washington, D.C.; Hrushesky, William, J. M., Dorn Veterans Affairs Medical Center, Columbia, South Carolina; Clayman, Gary, University of Texas, MD Anderson Cancer Center, Houston, Texas; Nemechek, Andrew, Tulane Cancer Center, New Orleans, Louisiana; Guthrie, Troy H., Jr., University of Florida, Jacksonville, Florida; Trask, Douglas, University of Iowa Health Care, Iowa City, Iowa; Arquette, Matthew, Washington University School of Medicine, St. Louis, Missouri; and Villaret, Douglas, University of Florida, Gainesville, Florida; *A Phase III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intratumoral Administration of INGN 201 in Combination with Chemotherapy Versus Chemotherapy Alone in 288 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN).* Sponsor: Aventis Pharmaceuticals - Gencell Division

NIH/OBA Receipt Date: 9-22-00. Not Selected for RAC Public Review: 10-13-00

0009-413 (Closed) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Naked Plasmid/Tyrosinase cDNA/Intra-lymphnodal Injection

Weber, Jeffrey, Keck/USC School of Medicine, USC Norris Center and Hospital, Los Angeles, California; Smith II, John W., Earl A. Chiles Research Institute Providence Portland Medical Center, Portland, Oregon; and Johnson, Denise, Stanford University, Stanford, California; *A Phase I Dose Ranging Safety Study Using Intra-Nodal Delivery of a Plasmid DNA (Synchrotope TA2M) in Adult Stage IV Melanoma Patients.*

NIH/OBA Receipt Date: 9-29-00. Not Selected for RAC Public Review: 11-7-00
Study complete: 4-4-02

0010-414 (Open) Gene Therapy/Phase I-II/Cancer/Hepatocellular Carcinoma/In Vitro/Autologous Dendritic Cells/Adenovirus/Alpha Fetoprotein/Intravenous Infusion

Economou, James S., Glapsy, John A., and McBride, William H., UCLA Medical Center, Los Angeles, California; *A Phase I/II Trial Testing Alpha-Fetoprotein (AFP) Genetic Immunization in Hepatocellular Carcinoma.*

NIH/OBA Receipt Date: 10-2-00. Not Selected for RAC Public Review: 10-23-00

0010-415 (Open) Gene Therapy/Phase II/Cancer/Ovarian/Oncogene-Regulation/In Vivo/Cationic Liposome Complex/DC-Chl-DOPE/E1A/Intraperitoneal Administration

Ueno, Naoto, University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase II Study of Intraperitoneal E1A-Lipid Complex for Patients with Advanced Epithelial Ovarian Cancer without HER-2/neu Overexpression.* Sponsor: Targeted Genetics Corporation

NIH/OBA Receipt Date: 10-6-00. Not Selected for RAC Public Review: 11-2-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0010-416 (Open) Gene Therapy/Phase II/Cancer/Ovarian/Oncogene-Regulation/In Vivo/Cationic Liposome Complex/DC-Chl-DOPE/E1A/Intraperitoneal Administration

Ueno, Naoto, University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase II Study of Intraperitoneal E1A-Lipid Complex for Patients with Advanced Epithelial Ovarian Cancer with HER-2/neu Overexpression.* Sponsor: Targeted Genetics Corporation

NIH/OBA Receipt Date: 10-6-00. Not Selected for RAC Public Review: 11-2-00

0010-417 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Colorectal/Hepatic Metastasis/Dominant Negative Mutation/In Vivo/Retrovirus/dnG1 Cyclin/Hepatic Arterial Infusion

Lenz, Heinz-Josef, Norris Cancer Center, University of Southern California, Los Angeles, California; *Tumor Site Specific Phase I/II Evaluation of Safety and Efficacy of Hepatic Arterial Infusion of a Matrix-Targeted Retroviral Vector Bearing a Dominant Negative Cyclin G1 (dnG1) Construct as Treatment for Colorectal Carcinoma Metastatic to Liver.*

NIH/OBA Receipt Date: 10-13-00. Publicly Reviewed at the December 2000 RAC meeting

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0010-418 (Open) Gene Therapy/Phase II/Cancer/Prostate/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Percutaneous Transperineal Intraprostatic Injection

Pollack, Alan, The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Randomized Phase II Study of Ad5CMV-p53 plus Radioactive Seed Implant vs Seed Implant Alone for PSA Relapse after External Beam Radiotherapy for Prostate Cancer.* Sponsor: Introgen Therapeutics, Inc.

NIH/OBA Receipt Date: 10-16-00. Not Selected for RAC Public Review: 11-7-00

0010-419 (RAC Reviewed with Recommendations) Gene Therapy/Cancer/Melanoma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/fhVII/hFc cDNA/Intratumoral Injection

Deisseroth, Albert, Yale University School of Medicine, New Haven Connecticut; *Intratumoral Injections of a Replication-Incompetent Adenoviral Vector Encoding a Factor VII Immunoconjugate to Induce a Cytolytic Immune Response against Melanoma Tumors: A Pilot Trial.*

NIH/OBA Receipt Date: 10-18-00. Publicly Reviewed at the December 2000 RAC meeting

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0010-420 (Open) Gene Therapy/Phase I-II/Other Disorders/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Crystal, Ronald G, Cornell University Medical College, New York, New York; and Rosengart, Todd, Evanston Northwestern Healthcare, Evanston, Illinois; *Phase I/II, Prospective, Placebo Controlled, Randomized Assessment of Direct Administration of a Replication Deficient Adenovirus Vector (Ad_{cu}VEGF121.1) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Diffuse Coronary Artery Disease as an Adjunct to Coronary Bypass Surgery.*

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-421 (Open) Gene Therapy/Phase I/Other Disorders/Ulcer/In Vivo/Adenovirus/Serotype 5/Platelet Derived Growth Factor (PDGF) cDNA/Intra Ulcer Administration

Mozingo, David, University of Florida College of Medicine, Gainesville, Florida; *A Dose Escalating Phase I Study of AdPDGF-B/GAM in the Treatment of Diabetic Ulcers of the Lower Extremity.* Sponsor: Selective Genetics, Inc.

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-422 (Open) Gene Therapy/Phase I/Infectious Diseases/HIV-1/Replication Inhibition/Single Chain Antibody Gene/In Vitro/Autologous Peripheral Blood Lymphocytes/Retrovirus/sFvhutat2 ant-HIV-1 Tat Protein Antibody/Intravenous Infusion

Marasco, Wayne, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Pilot Study to Evaluate the Safety and Effects of Autologous Lymphocytes Transduced with a Human Single-Chain Antibody Directed against the HIV-1 Tat Protein in HIV-1 Infected Human Subjects with Advanced Disease.*

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-423 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Monogenic Diseases/Junctional Epidermolysis Bullosa/In Vitro/Autologous Keratinocytes/Retrovirus/Laminin 5-beta3 cDNA/Skin Graft

Kimball, Alexa B., Stanford University Medical Center; *Laminin 5 Beta 3 Gene Therapy for Junctional Epidermolysis Bullosa.*

NIH/OBA Receipt Date: 10-18-00. Publicly Reviewed at the December 2000 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0010-424 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Muscle Cells/Plasmid DNA/Poloxamer 188/Del-1 cDNA/ Intramuscular Injection

Hinohara, Tomoaki, Cardiovascular Medicine and Coronary Interventions, Redwood City, California; Litt, Marc R., Jacksonville Heart Center, Jacksonville, Florida; Karlsberg, Ronald P., Cardiovascular Research Institute, Beverly Hills, California; Schaer, Gary L., Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; Piana, Robert, Vanderbilt University Medical Center, Nashville, Tennessee; and Jaff, Michael, The Heart and Vascular Institute of New Jersey, Morristown, New Jersey; *Developmentally Regulated Endothelial Locus (Del-1) Gene Medicine (VLTS-589) A Phase I Multi-Center, Open-Label, Single-Dose Escalation Clinical Safety Trial of VLTS-589 for the Treatment of Patients with Peripheral Arterial Disease.* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-425 (Under Review) Gene Therapy/Phase I/Other Disorders/Bone Fracture/In Vivo/Plasmid DNA/Collagen Sponge/Parathyroid Hormone cDNA/Bone Administration

Goulet, James Alan, University of Michigan; *A Prospective, Randomized Study to Assess the Safety of MAT-100 in Open Tibia Fractures Requiring an Intramedullary Rod (Phase I).* Sponsor: EBI, L.P./Biomed, Inc. and Selective Genetics, Inc.

NIH/OBA Receipt Date: 10-18-00. Review at a RAC meeting pending; sponsor has requested postponement of public review.

0010-426 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/In Vivo/Adenovirus Serotype 5/Replication-Competent Virus/Osteocalcin Promoter/Intratumoral Injection

Gardner, Thomas A., Indiana School of Medicine, Indianapolis, Indiana; *A Phase I Study of Intratumoral Injections of OCaP1 for Metastatic or Locally Recurrent Prostate Cancer, Part 1: Dose Finding, Part 2: Index Lesion Escalation.* Sponsor: DirectGene, Inc.

NIH/OBA Receipt Date: 10-18-00. Publicly Reviewed at the December 2000 RAC meeting

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0010-427 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Adenovirus Serotype 5/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Intradermal Administration

Crystal, Ronald G., Cornell University Medical College, New York, New York; *Effect of $Ad_{GV}CFTR.10$ on the Cystic Fibrosis Phenotype.*

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-428 (Open) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/Pro-Drug/In Vivo/Adenovirus Serotype 5/Replication-Competent Virus/Cytosine Deaminase cDNA/Herpes Simplex Virus Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Kim, Jae Ho and Freytag, Svend, Henry Ford Health System, Detroit, Michigan; *Phase I Study of Intraprostatic Administration of a Replication-Competent, Oncolytic Adenovirus Using Various Vector formulations to Patients with Localized Prostate Cancer Prior to Radical Prostatectomy.*

NIH/OBA Receipt Date: 10-18-00. Not Selected for RAC Public Review: 11-7-00

0010-429 (Open) Gene Therapy/Phase I/Cancer/Head and Neck Squamous Cell Carcinoma (SCCHN)/Immunotherapy/In Vivo/Fowlpox Virus/B7.1 (CD 80)/ICAM-1/LFA-3/Intratumoral Injection

Van Waes, Carter, National Institutes of Health, Bethesda, Maryland; *Phase I/Pilot Study of Intralesional Immunotherapy with a Recombinant Avipox Virus Engineered to Express a Triad of Co-stimulatory Molecules in Patients with Advanced Squamous Cell Carcinoma of the Head and Neck.*

NIH/OBA Receipt Date: 10-26-00. Not Selected for RAC Public Review: 5-10-01

0011-430 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/Serotype-5/Interleukin-7 cDNA/Intratumoral Injection

Dubinett, Steven M., UCLA School of Medicine, Los Angeles, California; *A Phase I/II Trial Evaluating Intratumoral Injection of Interleukin-7 Gene Modified Autologous Dendritic Cells for the Treatment of Non-Small Cell Lung Cancer.*

NIH/OBA Receipt Date: 11-1-00. Not Selected for RAC Public Review: 11-22-00

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0011-431 (Open) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Autologous Tumor Cells/Cationic Liposome Complex/DMRIE-DOPE/Vical-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral Injection

Gonzalez, Rene, University of Colorado Health Sciences Center; and Whitman, Eric D., Missouri Baptist Medical Center; The Melanoma Center of St. Louis, St. Louis, Missouri; Amatruda, Thomas, North Memorial Health Care/Hubert H. Humphrey Cancer Center, Robbinsdale, Minnesota; Morse, Michael, Duke University Medical Center, Durham, North Carolina; Atkins, Michael B., Beth Israel Deaconess Medical Center, Boston, Massachusetts; Bedikian, Agop Y., The University of Texas, MD Anderson Cancer Center, Houston, Texas; Lutzky, Jose, Mt. Sinai Comprehensive Cancer Center, Miami, Florida; Hutchins, Laura, University of Arkansas for Medical Sciences and Central Arkansas Veteran's Healthcare System, Little Rock, Arkansas; Schwarzenberger, Paul, Louisiana State University Health Sciences Center Lions Clinic, and the Medical Center of Louisiana at New Orleans, New Orleans, Louisiana; Patel, Ravi Comprehensive Blood and Cancer Center, Bakersfield, California; Thant, Myo, Maryland Hematology/Oncology Associates, Baltimore, Maryland; Thompson John A., University of Washington Medical Center and the Seattle Cancer Care Alliance, Seattle Washington; Galanis, Evanthia, Mayo Clinic, Rochester, Minnesota; Ernstoff, Marc, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Richards, Jon M., Oncology Specialities, S. C., Park Ridge, Illinois; Klencke, Barbara, University of California, San Francisco Comprehensive Cancer Center at Mount Zion, San Francisco, California; Hersh, Evan M., Arizona Cancer Center, Tucson, Arizona; and Blum, Ronald, Beth Israel Medical Center, New York, New York; *A Phase II Study of High-Dose Allovectin-7 in Patients with Advanced Metastatic Melanoma.* Sponsor: Vical Inc.

NIH/OBA Receipt Date: 11-16-00. Not Selected for RAC Public Review: 12-7-00

0011-432 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Immunotherapy/In Vivo/Cationic Liposome Complex/DMRIE-DOPE.Vical-1005/HLA-B7/Beta-2 Microglobulin cDNA/Intratumoral Injection

Gleich, Lyon, University of Cincinnati Medical Center, Cincinnati, Ohio; Khan, Mumtaz, Henry Ford Health System, Detroit, Michigan; Wolf, Gregory T., University of Michigan Health System, Ann Arbor, Michigan; Stenson, Kerstin M., The University of Chicago, Chicago, Illinois; Weinstein, Gregory, The Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; Lavertu, Pierre, Case Western University, University Hospitals of Cleveland, Cleveland, Ohio; Carroll, William, University of Alabama-Birmingham, Birmingham, Alabama; Hanna, Ehab, University of Arkansas for Medical Sciences, Little Rock, Arkansas; McCaffrey, Thomas, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; and Friedlander, Paul, Louisiana State University Health Sciences Center, New Orleans, Louisiana; *A Phase II Study of Safety and Efficacy of Allovectin-7 Immunotherapy for the Treatment of Primary Resectable Squamous Cell Carcinoma of the Oral Cavity or Oropharynx.* Sponsor: Vical Inc.

NIH/OBA Receipt Date: 11-16-00. Not Selected for RAC Public Review: 12-7-00

0011-433 (Open) Gene Marking/Cancer/Acute or Chronic Myelogenous Leukemia, Non-Hodgkin's Lymphoma, Myelodysplastic Syndrome/In Vitro/Epstein-Barr Virus Specific Allogeneic Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Bone Marrow Transplantation

Brenner, Malcolm, Baylor College of Medicine, Houston, Texas; *A Phase I Trial Evaluating the Use of RFT5-dgA to Deplete Alloreactive Cells Prior to Haploidentical Stem Cell Transplantation.*

NIH/OBA Receipt Date: 11-27-00. Not Selected for RAC Public Review: 12-15-00

0011-434 (Open) Gene Therapy/Phase I/Cancer/Various Types/Immunotherapy/In Vitro/Allogeneic Fibroblasts/Lethally Irradiated/Plasmid DNA/Interleukin-2 cDNA/Intratumoral Injection

Sobol, Robert E., Sidney Kimmel Cancer Center, San Diego, California; *A Phase I Study of Intra-Tumoral Injection with Allogeneic Fibroblasts Genetically Modified to Secrete IL-2 in Patients with Cancer Who Have Failed Standard Therapy*

NIH/OBA Receipt Date: 11-27-00. Not Selected for RAC Public Review: 12-22-00

0011-435 (Open) Gene Therapy/Phase I-II/Cancer/Myeloma/Immunotherapy/In Vitro/Allogeneic K562 Cells/Combination with Untransduced Tumor Cells/Plasmid DNA/GM-CSF cDNA/Intradermal Injection

Borrello, Ivan, Johns Hopkins University School of Medicine, Baltimore, Maryland; *Vaccination in Peripheral Stem Cell Transplant Setting for Multiple Myeloma: The Use of Autologous Tumor Cells with an Allogeneic GM-CSF Producing Bystander Cell Line.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 11-29-00. Not Selected for RAC Public Review: 12-28-00

0012-436 (Open) Gene Therapy/Phase I/Cancer/Glioma/Immunotherapy/In Vitro/Autologous Fibroblasts/In Combination with Untransduced Autologous Tumor and Dendritic Cells/Interleukin-4 cDNA/Intradermal Injection

Okada, Hideho, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; *Gene Therapy of Malignant Gliomas: A Pilot Study of Vaccination with Autologous Glioma-Lysate and Dendritic Cells Admixed with IL-4 Transduced Fibroblasts to Elicit an Immune Response.*

NIH/OBA Receipt Date: 12-5-00. Not Selected for RAC Public Review: 12-27-00

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0012-437 (Open) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vivo/Adenovirus/Serotype 5/CD40 Ligand cDNA/Intratumoral Injection

Harvey, Ben-Gary and Crystal, Ronald G., New York Presbyterian Hospital-Weill Medical College, Cornell University, New York, New York; *In Vivo Transfer of the CD40 Ligand Gene to Primary Lung Tumors to Activate Dendritic Cells and Induce Anti-Tumor Immunity.*

NIH/OBA Receipt Date: 12-7-00. Not Selected for RAC Public Review: 12-28-00

0012-438 (Open) Gene Therapy/Cancer/Head and Neck Squamous Cell Carcinoma/Oncogene Regulation/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intratumoral Injection

Arseneau, James C., Albany Regional Cancer Center, Albany, New York; Berman, Barry S., Cancer Centers of Florida, Orlando, Florida; Anthony, Stephen P., Cancer Care Northwest, Spokane, Washington; Richards, Donald A., Tyler Cancer Center, Tyler, Texas; and Nemunaitis, John and Senzer, Neil, US Oncology, Dallas, Texas; *A Multicenter, Phase II Study of Intratumoral Injections of E1A-Lipid Complex and Re-Irradiation for Treatment of Patients with Recurrent Head and Neck Squamous Cell Carcinoma.* Sponsor: Targeted Genetics

NIH/OBA Receipt Date: 12-22-00. Not Selected for RAC Public Review: 3-2-01

0012-439 (Open) Gene Therapy/Phase I/Other/Peripheral Artery Disease/In Vivo/Ischemic Lower Limb/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Intramuscular Injection

Crystal, Ronald G., Weill Medical College, Cornell University, New York, New York; *Gene Therapy in Conjunction with Operative Bypass Grafting for Severe Peripheral Vascular Ischemia in Individuals with Insulin-Dependent Diabetes.*

NIH/OBA Receipt Date: 12-26-00. Not Selected for RAC Public Review: 1-16-01

0101-440 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Plasmid DNA/Murine gp75 Melanoma Antigen/Intramuscular Injection

Wolchok, Jedd D., Memorial Sloan Kettering Cancer Center, New York, New York; *Phase I Study of gp75 DNA Vaccine in Patients with AJCC Stage III and IV Melanoma.* Sponsor: ImClone Systems, Inc.

NIH/OBA Receipt Date: 1-3-01. Not Selected for RAC Public Review: 1-24-01

0101-441 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Vaccinia Virus/B7.1 (CD80)/ICAM-1/LFA-3/Intratumoral Injection

Kaufman, Howard L., Columbia University, New York, New York; *A Phase I Trial of Intralesional rV-TRICOM Vaccine in the Treatment of Malignant Melanoma.*

NIH/OBA Receipt Date: 1-4-01. Not Selected for RAC Public Review: 1-26-01

0101-442 (Open) Gene Therapy/Phase I-II/Other/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Vascular Endothelial Growth Factor cDNA/Cardiac Administration

Crystal, Ronald G., Weill Medical College, Cornell University, New York, New York; and Rosengart, Todd K., Evanston Northwestern Healthcare, Evanston, Illinois; *Phase I/II, Prospective Placebo Controlled, Randomized Assessment of Adenoviral Mediated VEGF121 cDNA Myocardial Angiogenesis Therapy as an Adjunct to Individuals with Diffuse Coronary Artery Disease Undergoing Off-Pump Coronary Artery Bypass Surgery.*

NIH/OBA Receipt Date: 1-9-01. Not Selected for RAC Public Review: 1-30-01

0101-443 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/Antisense TAR/Antisense tat-rev/In Vitro/CD34+ Cells/Intravenous

Laurence, Jeffrey C., Cornell University Medical College, New York, New York; *Evaluation of the Safety and Effects of ex vivo Modification and Re-Infusion of CD34+ Cells by an Antisense Construct Against HIV-1 in a Retrovirus Vector.* Sponsor: Enzo Therapeutics, Inc.

NIH/OBA Receipt Date: 1-10-01. Publicly Reviewed at the March 2001 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0101-444 (Open) Gene Therapy/Phase I/Coronary Artery Disease/In Vivo/Muscle Cells/Plasmid DNA/Poloxamer 188/Del-1 cDNA/ Retrograde Intravenous (rIV) Injection into the Heart

Dreiling, Roger J., Cardiovascular Consultants of Oregon, Corvallis, Oregon; *A Phase I Multi-Center, Open-Label, Single-Dose Escalation Clinical Trial of VLTS-589 for Treatment of Patients with Coronary Artery Disease.* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 4-20-01

0101-445 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Clayman, Gary, The University of Texas MD Anderson Cancer Center, Houston, Texas; *Clinical Protocol for Wild Type p53 Gene Induction in Premalignancies of Squamous Epithelium of the Oral Cavity Via an Adenoviral Vector.* Sponsor: Introgen Therapeutics, Inc.

NIH/OBA Receipt Date: 1-10-01. Publicly Reviewed at the March 2001 RAC meeting

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0101-446 (Open) Gene Therapy/Phase I/Monogenic Disease/Severe Combined Immune Deficiency Due to JAK3 Deficiency/In Vitro/Autologous CD34+ Cells from Peripheral Blood or Bone Marrow/Retrovirus/JAK3 cDNA/Intravenous Infusion

Sorrentino, Brian P. and Cunningham, John M., St. Jude Children's Research Hospital, Memphis, Tennessee; and Buckley, Rebecca, Duke University School of Medicine, Durham, North Carolina; *Transplantation of Gene-Corrected Autologous CD34+ Hematopoietic Stem Cells in Previously Transplanted Patients with JAK3 Deficiency and Persistent Humoral Immune Defects.*

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-447 (Open) Gene Therapy/Phase I/Cancer/Prostate Cancer/In Vivo/Dendritic Cells/Adenovirus/Serotype 5/PSA cDNA/Subcutaneous Injection

Lubaroff, David, University of Iowa, Iowa City, Iowa; *Phase I Study of Adenovirus/PSA Vaccine in Men with Metastatic Prostate Cancer.*

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-448 (Open) Gene Therapy/Phase II-III/Cancer/Non-Small Cell Lung Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Swisher, Stephen, University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase II/III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intralesional Administration of RPR/INGN 201 in Combination with Taxotere® and Carboplatin and Radiotherapy Versus Taxotere® and Carboplatin and Radiotherapy Alone in Patients with Locally Advanced Unresectable Non-Small Cell Lung Cancer (NSCLC).* Sponsor: Introgen Therapeutics, Inc.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-449 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Interleukin-12 cDNA/Intratumoral Injection

Miles, Brian J., Baylor College of Medicine, Houston, Texas; *Phase I Study of Adenoviral Vector Delivery of the IL-12 Gene in Men with Local Recurrence of Prostate Cancer After Irradiation Therapy.*

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-450 (Open) Gene Therapy/Phase II/Cancer/Prostate Cancer/Vector Directed Cell Lysis/In Vivo/Autologous Tumor Cells/Adenovirus/Serotype 5/Replication Competent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen/Intratumoral Injection

DeWeese, Theodore, Johns Hopkins Oncology Center, Baltimore, Maryland; Roach III, Mack, University of California, San Francisco, San Francisco, California; and Michalski, Jeff, Washington University Medical School, Saint Louis, Missouri; *A Phase II Randomized Comparison Study of an Intraprostatic Injection of CV7606 Followed by External Beam Radiotherapy (EBRT) Versus EBRT Alone in Patients with Intermediate Risk, Clinically Localized Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0101-451 (Open) Gene Therapy/Phase II/Cancer/Prostate/Vector Directed Cell Lysis/In Vivo/Adenovirus/Serotype 5/Replication Competent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen/Intravenous Injection

Small, Eric, University of California, San Francisco, San Francisco, California; *A Randomized, Placebo Controlled Phase II Study of an Intravenous Injection of CV787, a Prostate-Specific Antigen Oncolytic Adenovirus, Plus Weekly Docetaxel in Patients with Metastatic Hormone Refractory Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-452 (Open) Gene Therapy/Phase IIb-III/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Adenovirus/Serotype 5/Fibroblast Growth Factor (FGF) cDNA/Intracoronary Administration

Grines, Cindy L., William Baumont Hospital, Royal Oak, Michigan; Bethala, Vasanth, Medical Research Institute, Slidell, LA; Erenrich, Norman, Florida Cardiovascular Research, Atlantis, FL; Gammon, Roger, Austin Heart, Austin, TX; Henry, Timothy, Abbott Northwestern Hospital, Minneapolis, MN; Licandro, Rudolph, Louisville Cardiology Medical Group, Louisville, KY; Saucedo, Jorge, University of Arkansas for Medical Sciences, Little Rock, AR; Tonkon, Melvin, Anaheim Heart and Research Institute, Santa Ana, CA; Watkins, Matthew , The University of Vermont, Burlington, VT; Grossman, P. Michael, The University of Michigan Health System, Ann Arbor, Michigan; Butman, Samuel, University Medical Center, University of Arizona, Tucson, Arizona; Churchill, David A., Washington Regional Medical Center, Fayetteville, Arkansas; Conn, Eric H., The Chattanooga Heart Institute, Chattanooga, Tennessee; Coppola, John T., Saint Vincent Catholic Medical Centers of New York, New York, New York; Fuchs, Shmuel, Washington Hospital Center, Washington, D.C.; Ghali, Jalal K., Cardiac Centers of Louisiana, Shreveport, Louisiana; Hodes, Zachary I., The Care Group, LLC, Indianapolis, Indiana; Nadar, Venkatesh K., Heritage Cardiology Associates, Camp Hill, Pennsylvania; Rowe, Steven K., Heartland Regional Medical Center, St. Joseph, Missouri; Brennan, Theresa, University of Iowa Healthcare, Iowa City, Iowa; Browne, Jr., Kevin F., Watson Clinic LLP, Lakeland, Florida; Dib, Nabil, Arizona Heart Institute, Phoenix, Arizona; Ellis, Stephen, Cleveland Clinic Foundation, Cleveland, Ohio; Hart, Kevin, Stucky Research Center, Fort Wayne, Indiana; Iskandrian, Ami E., University of Alabama at Birmingham, Birmingham, Alabama; Kleiman, Neal S., Baylor College of Medicine, Houston, Texas; Marmur, Jonathan, Mount Sinai Hospital, New York, New York; Marshall, J. Jeffrey, Crawford Long Hospital, Atlanta, Georgia; Penny, William F., San Diego VA Medical Center, San Diego, California; Pepine, Carl J., University of Florida, Gainesville, Florida; Saenz, Carlos and Taussig, Andrew, Florida Hospital, Orlando, Florida; Schaer, Gary L., Rush-Presbyterian St. Luke's Medical Center, Chicago, Illinois; Sequeira, Rafael F., University of Miami-Jackson Memorial Hospital, Miami, Florida; Baran, Kenneth W., United's John Nasseff Heart Hospital, Saint Paul, Minnesota; Helmer, Gregory A., Minnesota Heart Clinic, P.A., Edina, Minnesota; Mendelsohn, Farrell O., Cardiology, P.C., Birmingham, Alabama; Moran, John F., Loyola University Medical Center, Maywood, Illinois; Sanborn, Timothy, Evanston Northwestern Healthcare, Evanston, Illinois; Sharaf, Barry L., Rhode Island Hospital, Providence, Rhode Island; Moreyra, Abel E., Robert Wood Johnson Medical School, New Brunswick, New Jersey; Cohen, Eric, Cardiovascular Associates, P.C., Birmingham, Alabama; Lee, Joon, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Levine, Glenn, Houston VA Medical Center, Houston, Texas; Lopez, John, University of Chicago Medical Center, Chicago, Illinois; McGrew, Frank, III, The Stern Cardiovascular Center, Memphis, Tennessee; Thai, Hoang, Southern Arizona Veterans Affairs Health Care System, Tucson, Arizona; Zabalgotia, Miguel, The University of Texas Health Science Center at San Antonio; San Antonio, Texas; Laham, Roger, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Murphy, Patrick, L., The Heart Group, PC, Mobile, Alabama; Rade, Jeffrey J., Johns Hopkins University School of Medicine, Baltimore, Maryland; Simari, Robert D., Mayo Clinic, Rochester, Minnesota; Savage, Michael P., Jefferson Heart Institute, Philadelphia, Pennsylvania; Zoble, Robert G., James A. Haley Veterans Hospital, Tampa, Florida; Kellett, Mirle, Maine Medical Center, Portland, Maine; Moreyra, Abel, Robert Wood Johnson University Hospital, New Brunswick, New Jersey; Niles, Nathaniel, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Ohman, Erik, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and Murray, Conrad, Global Cardiovascular Associates, Inc., Las Vegas, Nevada; *A Multicenter, Randomized, Double-Blind, Placebo Controlled, Dose-Response Study to Evaluate the Efficacy and Safety of Ad5.1FGF-4 in Patients with Stable Angina.* Sponsor: Berlex Laboratories.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

0101-453 (Open) Gene Therapy/Phase I/Cancer/Glioblastoma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Human Interferon-beta cDNA/Stereotactic Injection

Eck, Stephen L., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Rosenfeld, Steven S., University of Alabama at Birmingham, Birmingham, Alabama; Chiocca, E. Antonio, Massachusetts General Hospital, Boston, Massachusetts; Hamilton, Allan, University of Arizona, Tucson, Arizona; and Lillehei, Kevin, University of Colorado Health Sciences Center, Denver, Colorado; *A Multi-Center, Open Label, Two Part, Dose Escalation Study to Determine the Tolerability of Interferon-beta Gene Transfer in the Treatment of Recurrent or Progressive Glioblastoma Multiforme.* Sponsor: Biogen.

NIH/OBA Receipt Date: 1-12-01. Not Selected for RAC Public Review: 1-31-01

0101-454 (Open) Gene Therapy/Phase II/Cancer/Head and Neck Squamous Cell Carcinoma/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Yoo, George H., Wayne State University, Detroit, Michigan; *Phase II Trial of Surgery with Perioperative RPR/INGN 201 (Ad5CMV-p53) Gene Therapy Followed by Chemoradiotherapy for Advanced Resectable Squamous Cell Carcinoma of the Oral Cavity and Oropharynx.* Sponsor: Southwest Oncology Group.

NIH/OBA Receipt Date: 1-10-01. Not Selected for RAC Public Review: 1-31-01

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0101-455 (Open) Gene Therapy/Phase II/Cancer/Breast/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5/p53 cDNA/Intratumoral Injection

Cristofanilli, Massimo, The University of Texas MD Anderson Cancer Center, Houston, Texas; *Phase II, Single Arm, Single Institution Clinical Trial of Docetaxel and Doxorubicin in Combination with Local Administration of Ad5CMV-p53 (RPR/INGN-201) in Locally Advanced Breast Cancer (LABC).* Sponsor: Introgen Therapeutics, Inc.

NIH/OBA Receipt Date: 1-16-01. Not Selected for RAC Public Review: 1-31-01

0101-456 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vivo/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD 80)/ICAM-1/LFA-3/GM-CSF/Intramuscular or Intradermal Injection

von Mehren, Margaret, Fox Chase Cancer Center, Philadelphia, Pennsylvania; *Phase I Study of a Recombinant Fowlpox Vaccine rF-CEA(6D)/TRICOM alone or with GM-CSF in Patients with Advanced CEA Expressing Adenocarcinoma.*

NIH/OBA Receipt Date: 1-25-01. Not Selected for RAC Public Review: 2-27-01

0101-457 (Open) Gene Therapy/Phase I/Cancer/Soft Tissue Sarcoma/In Vivo/Adenovirus/Type 5/Tumor Necrosis Factor cDNA/Intratumoral Injection

Hanna, Nader, University of Kentucky Chandler Medical Center, Lexington, Kentucky; Nemunaitis, John, US Oncology, Dallas, Texas; Sandler, Alan B., Vanderbilt University, Nashville, Tennessee; Vijayakumar, Srinivasan and Warso, Michael, University of Illinois at Chicago, Chicago, Illinois; Mundt, Arno, University of Chicago, Chicago, Illinois; and Richards, Donald A., Tyler Cancer Center, Tyler, Texas; *An Open-Label, Phase I, Dose-Escalation Study of TNFerade™ Biologic with Radiation Therapy as an Adjunct to Surgery or for Palliation of Soft Tissue Sarcoma of the Extremities.* Sponsor: GenVec.

NIH/OBA Receipt Date: 1-29-01. Not Selected for RAC Public Review: 2-26-01

0102-458 (Open) Gene Therapy/Phase II/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vivo/Canarypox Virus/Carcinoembryonic Antigen/B 7.1 (CD80)/Intramuscular and Intradermal Injections

Kaufman, Howard L., Columbia University, New York, New York; von Mehren, Margaret, Fox Chase Cancer Center, Philadelphia, Pennsylvania; Conry, Robert M., The University of Alabama at Birmingham, Birmingham, Alabama; Marshall, John, Georgetown University Medical Center, Washington D.C.; Heim, William J., Hematology & Oncology Associates of Northeastern PA, Dunmore, Pennsylvania; Lenz, Heinz-Josef, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California; Kindler, Hedy, The University of Chicago, Chicago, Illinois; Garrett, Christopher, H. Lee Moffitt Cancer Center, Tampa, Florida; and Urba, Walter, Providence Portland Medical Center, Portland, Oregon; *Pilot Phase II Study of Safety and Immunogenicity of a ALVAC-CEA/B7.1 Vaccine Administered with Chemotherapy, Alone or in Combination with Tetanus Toxoid, as Compared to Chemotherapy Alone, in Patients with Metastatic Colorectal Adenocarcinoma.* Sponsor: Aventis Pasteur Limited.

NIH/OBA Receipt Date: 2-15-01. Not Selected for RAC Public Review: 4-12-01

0103-459 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Adeno-Associated Virus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Corman, John M., Virginia Mason Medical Center, Seattle, Washington; *A Phase I Dose Escalation Study of Human GM-CSF Gene Transduced Irradiated Allogeneic Prostate Cancer Cell Vaccine (GVAX® Prostate Cancer Vaccine (PC-3)) in Patients with Hormone-Refractory Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 3-6-01. Not Selected for RAC Public Review: 7-27-01

0103-460 (Open) Gene Therapy/Phase I/Cancer/Chronic Lymphocytic Leukemia/Non-Hodgkin's Lymphoma/Immunotherapy/In Vitro/Autologous Lymphoma Cells/Adenovirus/Serotype 5/Interleukin-2 cDNA/CD40 Ligand cDNA/Subcutaneous Injection

Takahashi, Satoshi and Brenner, Malcolm, Baylor College of Medicine, Houston, Texas; *Treatment of Chronic Lymphocytic Leukemia (CLL) with IL-2 Gene Modified and Human CD40 Ligand-Expressing Autologous Tumor Cells.*

NIH/OBA Receipt Date: 3-19-01. Not Selected for RAC Public Review: 4-6-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0104-461 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vivo/Plasmid DNA/Polyvinylpyrrolidone (PVP)/Interferon-alpha/Interleukin-12 cDNA/Intratumoral Injection

Posner, Marshall R., Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I/II Multi-Center, Open-Label, Multiple Administration Trial of the Safety, Tolerability, and Efficacy of an IFN-alpha/IL-12 Plasmid-Based Therapeutic.* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 4-9-01. Not Selected for RAC Public Review: 4-27-01

0104-462 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Pro-Drug/In Vivo/Tumor Cells/Salmonella typhimurium/E. coli Cytosine Deaminase cDNA/Intratumoral Injection/Combined with 5fluorocytosine

Nemunaitis, John J. and Cunningham, Charles, Mary Crowley Medical Research Center (US Oncology), Dallas, Texas; *A Phase I Trial of Genetically Modified Salmonella typhimurium Expressing Cytosine Deaminase (TAPET-CD, VNP20029) Administered by Intra-Tumoral Injection in Combination with 5-fluorocytosine for Patients with Advanced or Metastatic Cancer.* Sponsor: Vion Pharmaceuticals, Inc.

NIH/OBA Receipt Date: 4-16-01. Publicly Reviewed at the June 2001 RAC meeting.

0104-463 (Open) Gene Therapy/Phase I/Peripheral Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/Fibroblast Growth Factor 1 cDNA/Intramuscular Injection

Comerota, Anthony J., Temple University School of Medicine, Philadelphia, Pennsylvania; Henry, Tim, Hennepin County Medical Center, Minneapolis, Minnesota; and Chronos, Nicolas, Atlanta Cardiovascular Research Institute, Atlanta, Georgia; *Phase I Double Blind, Parallel-Group, Multi-Center, Gene Expression (Synthesis of FGF-1 mRNA), Safety and Tolerability Study of Increasing Single Doses of NV1FGF Administered by Intra-Muscular Injection in Patients with Severe Peripheral Artery Occlusive Disease (PAOD) Planned to Undergo Amputation Above the Ankle.* Sponsor: Aventis Pharma Recherche-Developpement.

NIH/OBA Receipt Date: 4-16-01. Not Selected for RAC Public Review: 5-4-01

0104-464 (Open) Gene Therapy/Phase I/Cancer/Prostate/Vector-Directed Cell Lysis/Replication-Competent Virus/Pro-Drug/In Vivo/Adenovirus/E. coli Cytosine Deaminase cDNA/5-Fluorocytosine/Herpes Simplex Thymidine Kinase cDNA/Ganciclovir/Intratumoral Injection

Kim, Jae Ho and Freytag, Svend O., Henry Ford Health System, Detroit, Michigan; *Phase I Study of Combined Suicide Gene Therapy and Radiation Therapy for Locally Advanced Carcinoma of the Prostate.*

NIH/OBA Receipt Date: 4-17-01. Not Selected for RAC Public Review: 5-7-01

0104-465 (Open) Gene Therapy/Phase I/Monogenic Disease/Alpha-1 Antitrypsin Deficiency/In Vivo/Adeno-Associated Virus/Alpha-1 Antitrypsin cDNA/Intramuscular Injection

Flotte, Terence R., University of Florida, Gainesville, Florida; *A Phase I Trial of Intramuscular Injection of a Recombinant Adeno-Associated Virus Alpha-1-Antitrypsin (rAAV-AT) Gene Vector to AAT-Deficient Adults.*

NIH/OBA Receipt Date: 4-18-01. Not Selected for RAC Public Review: 5-8-01

0104-466 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Chemoprotection/In Vivo/Cationic Liposome Complex/Cholesterol/DOTIM/Manganese Super Oxide Dismutase (MnSOD)/Intraesophageal Administration

Belani, Chandra P., University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; *Concurrent Chemotherapy (Paclitaxel and Carboplatin) and Thoracic Radiotherapy with Swallowed Manganese Superoxide Dismutase (MnSOD) Plasmid Liposome (PL) Protection in Patients with Locally Advanced Stage III Non-Small Cell Lung Cancer. A Phase I-II Study.*

NIH/OBA Receipt Date: 4-18-01. Not Selected for RAC Public Review: 5-8-01

0104-467 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Other/Peripheral Neuropathy/In Vivo/Endothelial Cells/Plasmid DNA/$VEGF_{165}$ cDNA/Intramuscular Injection

Isner, Jeffrey, St. Elizabeth's Medical Center, Boston, Massachusetts; *VEGF Gene Transfer for Diabetic Neuropathy.*

NIH/OBA Receipt Date: 4-18-01. Publicly Reviewed at the June 2001 RAC meeting.

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0104-468 (Open) Gene Therapy/Phase I-II/Coronary Artery Disease/In Vivo/Endothelial Cells/Plasmid DNA/VEGF$_{165}$ cDNA/Intramyocardial Injection

McCarthy, Patrick, The Cleveland Clinic Foundation, Cleveland, Ohio; *VEGF Gene Transfer to Promote Angiogenesis in Patients with Advanced Heart Failure.*

NIH/OBA Receipt Date: 4-18-01. Not Selected for RAC Public Review: 5-8-01

0104-469 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Other/Parkinson's Disease/In Vivo/Adeno-Associated Virus/Glutamic Acid Decarboxylase 65-67 cDNA/Intracerebral Administration

During, Matthew J., Jefferson Medical College, Philadelphia, Pennsylvania and Kaplitt, Michael, New York Hospital-Weill Medical College of Cornell University, New York, New York; *Subthalamic GAD Gene Transfer in Parkinson Disease Patients Who Are Candidates for Deep Brain Stimulation.*

NIH/OBA Receipt Date: 4-18-01. Publicly Reviewed at the June 2001 RAC meeting.

0104-470 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Osteosarcoma Metastasis to Lung/Vector-Directed Cell Lysis/In Vivo/Adenovirus Serotype 5/Replication-Competent Virus/Promoter of Osteocalcin/Intravenous Injection

Meyers, Paul A., Memorial Sloan-Kettering Cancer Center, New York, New York and Reaman, Gregory H., George Washington University School of Medicine and Children's National Medical Center, Washington, D.C.; *A Phase I/II Dose Escalation and Activity Study of Intravenous Injections of OCaP1 in Subjects with Refractory Osteosarcoma Metastatic to Lung.* Sponsor: DirectGene, Inc.

NIH/OBA Receipt Date: 4-18-01. Publicly Reviewed at the June 2001 RAC meeting.

0104-471 (Open) Gene Therapy/Cancer/Breast Cancer/In Vivo/Tumor Suppressor/Adenovirus/Melanoma Differentiation Associated Protein-7 cDNA/Intratumoral Injection

Buchholz, Thomas A., MD Anderson Cancer Center, Houston, Texas; *A Phase I/II Dose-Escalation Trial of Intratumoral Injection with a Replication-Deficient Adenovirus Vector, Ad-mda7 (INGN 241), in Combination with Radiation Therapy in Patients with Locally Recurrent Breast Cancer.* Sponsor: Introgen Therapeutics, Inc.
NIH/OBA Receipt Date: 4-18-01. Not Selected for RAC Public Review: 5-8-01

0105-472 (Open) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vitro/Allogeneic K562 Cells/Combination with Untransduced Tumor Cells/Plasmid DNA/GM-CSF cDNA/Intradermal Injection

Smith II, John W., Providence Portland Medical Center, Portland, Oregon; Aboulafia, David, Virginia Mason Medical Center, Seattle, Washington; Sternman, Daniel H., University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; and Jablons, David M., University of California, San Francisco, San Francisco, California; *Phase I/II Study of Vaccination with Irradiated Autologous Lung Tumor Cells Mixed with a GM-CSF Secreting Bystander Cell Line (Lung Bystander GVAX®) in Advanced Non-Small Cell Lung Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 5-14-01. Not Selected for RAC Public Review: 6-4-01

0105-473 (Open) Gene Marking/Cancer/EBV-Positive Hodgkin Disease/In Vitro/LMP2A-Specific Cytotoxic T Lymphocytes/Retrovirus/Neomycin Phosphotransferase cDNA/Adenovirus/LMP2A cDNA/Intravenous Administration

Gahn, Benedikt, Heslop, Helen, and Rooney, Cliona, Baylor College of Medicine, Houston, Texas; *Administration of Neomycin Resistance Gene Marked LMP2A-Specific Cytotoxic T Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin's Lymphoma.*

NIH/OBA Receipt Date: 5-14-01. Not Selected for RAC Public Review: 6-4-01

0105-474 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Plasmid DNA/Human and Mouse Prostate Specific Membrane Antigen cDNAs/Intramuscular Injection

Scher, Howard I., and Wolchok, Jedd, D., Memorial Sloan-Kettering Cancer Center, New York, New York; *Vaccination of Prostate Cancer Patients with Human and Mouse Specific Membrane Antigen (PSMA) DNA Vaccine: A Pilot Trial to Assess Safety and the Immune Response.*

NIH/OBA Receipt Date: 5-24-01. Not Selected for RAC Public Review: 6-14-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0106-475 (Open) Gene Therapy/Phase II/Cancer/Pancreas/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Plasmid/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Intradermal Injection

Jaffee, Elizabeth M., Johns Hopkins University School of Medicine, Baltimore, Maryland; *A Safety and Efficacy Trial of Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene in Combination with Adjuvant Chemotherapy for the Treatment of Adenocarcinoma of the Pancreas.*

NIH/OBA Receipt Date: 6-11-01. Not Selected for RAC Public Review: 6-29-01

0106-476 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) cDNA/Aerosol Administration

Virella-Lowell, Isabel, University of Florida, College of Medicine, Gainesville, Florida; *Evaluation of Anti-Inflammatory and Anti-Protease Pretreatment on the Delivery of Aerosolized tgAAVCF to Cystic Fibrosis Patients with Mild Lung Disease.* Sponsor: Targeted Genetics.

NIH/OBA Receipt Date: 6-11-01. Not Selected for RAC Public Review: 7-12-01

0106-477 (Open) Gene Therapy/Phase I/Cancer/Solid Tumors/Immunotherapy/In Vivo/Fowlpox Virus/B7.1 (CD80)/ICAM-1/LFA-3/Intratumoral Injection

Kaufman, Howard L., Albert Einstein College of Medicine, Bronx, New York; *Intra-Lesional rF-B7.1 Versus rF-TRICOM Vaccine in the Treatment of Metastatic Cancer.*

NIH/OBA Receipt Date: 6-12-01. Not Selected for RAC Public Review: 7-2-01

0106-478 (Open) Gene Therapy/Phase I/Cancer/CEA-Expressing Malignancies/Immunotherapy/In Vitro/Autologous Dendritic Cells/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD80)/ICAM-1/LFA-3/GM-CSF/Intravenous

Lyerly, H. Kim, Duke University Medical Center, Durham, North Carolina; *A Phase I Study of Active Immunotherapy with Autologous Dendritic Cells Infected with CEA-6D Expressing Fowlpox-TRICOM in Patients with Advanced or Metastatic Malignancies Expressing CEA.*

NIH/OBA Receipt Date: 6-28-01. Not Selected for RAC Public Review: 7-19-01

0106-479 (Open) Gene Therapy/Phase I-II/Cancer/Acute Myelogenous Leukemia/Immunotherapy/In Vitro/Allogeneic K562 Cells/Plasmid DNA/GM-CSF cDNA/Intradermal Injection

Borrello, Ivan, Johns Hopkins University School of Medicine, Baltimore, Maryland; Stock, Wendy, University of Chicago, Chicago, Illinois; Damon, Lloyd, University of California, San Francisco, San Francisco, California; and DeAngelo, Daniel, Dana Farber Cancer Institute, Boston, Massachusetts; *Vaccination in Peripheral Stem Cell Transplant Setting for Acute Myelogenous Leukemia: The Use of Autologous Tumor Cells with an Allogeneic GM-CSF Producing Bystander Cell Line.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 6-29-01. Not Selected for RAC Public Review: 7-20-01

0107-480 (RAC Reviewed with Recommendations) Gene Therapy/Phase IIb/Other/End Stage Renal Disease/Stenosis Prevention/In Vivo/Adenovirus/Vascular Endothelial Growth Factor D/Perivascular Collagen Collar Device

Fuster, Valentin, Mount Sinai Medical Center, New York, New York; *A Phase IIb, Randomized, Multicenter, Double-Blind Study of the Efficacy and Safety of Trinam™ (EG004) in Stenosis Prevention at the Graft-Vein Anastomosis Site in Dialysis Patients.* Sponsor: Ark Therapeutics, Ltd.

NIH/OBA Receipt Date: 7-6-01. Publicly Reviewed at the September 2001 RAC meeting.

0107-481 (Open) Gene Therapy/Phase Ib-II/Cancer/Brain Tumors/Malignant Glioma/Vector-Directed Cell Lysis/In Vivo/Herpes Simplex Virus Type 1/Tumor Lysis/Intracerebral Injection

Markert, James M., University of Alabama at Birmingham, Birmingham, Alabama; *An Open-Label, Phase Ib/II Study of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally to Subjects with Recurrent Malignant Glioma.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 7-9-01. Not Selected for RAC Public Review: 7-31-01

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0107-482 (Open) Gene Therapy/Phase Ib-II/Cancer/Brain Tumors/Malignant Glioma/Vector-Directed Cell Lysis/In Vivo/Herpes Simplex Virus Type 1/Tumor Lysis/Intracerebral Injection

Markert, James M., University of Alabama at Birmingham, Birmingham, Alabama; *Long-Term Follow-Up of the Safety and Survival of Subjects with Recurrent Malignant Glioma Who Enrolled in a Phase Ib/II Study (protocol 0107-481) of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 7-9-01. Not Selected for RAC Public Review: 7-31-01

0107-483 (Open) Gene Therapy/Phase Ib-II/Cancer/Brain Tumors/Malignant Glioma/Vector-Directed Cell Lysis/In Vivo/Herpes Simplex Virus Type 1/Tumor Lysis/Intracerebral Injection

Markert, James M., University of Alabama at Birmingham, Birmingham, Alabama; *Long-Term Follow-Up of the Safety and Survival of Subjects with Recurrent Malignant Glioma Who Enrolled in a Phase Ib/II Study (protocol 0107-481) of the Safety, Tolerability and Efficacy of G207, a Genetically Engineered Herpes Simplex Type-1 Virus, Administered Intracerebrally.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 7-9-01. Not Selected for RAC Public Review: 7-31-01

0107-484 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/In Vivo/Plasmid in Poly (DL-lactide-coglycolide) (PLG) Microparticles/Cytochrome P450 Isoenzyme 1B1 (CYP1B1) Gene/Intramuscular Injection

Gribben, John G., Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Open-Label Study of the Safety and Feasibility of Vaccinating Cancer Patients with Repeated Doses of ZYC300.* Sponsor: ZYCOS, Inc.

NIH/OBA Receipt Date: 7-11-01. Not Selected for RAC Public Review: 7-31-01

0107-485 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Breast/In Vitro/Autologous Bone Marrow Cells/Adenovirus/bcl-2 Dominant Negative Mutant/Bone Marrow Transplant

Clarke, Michael F., University of Michigan, Ann Arbor, Michigan; *Purging of Autologous Stem Cell Sources with bcl-x_s Adenovirus for Women Undergoing High-Dose Chemotherapy for Stage IV Breast Carcinoma.*

NIH/OBA Receipt Date: 7-11-01. Publicly Reviewed at the September 2001 RAC meeting.

0107-486 (Open) Gene Therapy/Phase II/Infectious Disease/Human Immunodeficiency Virus-1/Replication Inhibition/In Vitro/Autologous CD34+ Cells/Retrovirus/Hammerhead Ribozyme/Intravenous

Mitsuyasu, Ronald, UCLA Medical Center, Los Angeles, California; and Merigan, Thomas C., Jr., Stanford Medical Center, Stanford, California; *A Randomized Phase II, Double-Blind, Controlled Trial to Evaluate the Safety and Efficacy of Autologous CD34+ Hematopoietic Progenitor Cells Transduced with Either a Delivery Gene Construct (LNL6) or LNL6 that Contains an Anti-HIV-1 Ribozyme in Patients with HIV-1 Infection.* Sponsor: Johnson & Johnson Research Pty Limited.

NIH/OBA Receipt Date: 7-11-01. Not Selected for RAC Public Review: 7-31-01

0107-487 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Other/Age-related Macular Degeneration (AMD)/Adenovirus/Pigment-Epithelium Derived Factor (PEDF) cDNA/Intravitreal Administration

Campochiaro, Peter A., Johns Hopkins University School of Medicine, Baltimore, Maryland; *An Open-Label, Phase I, Single Administration, Dose Escalation Study of AD_{GV}PEDF.11D (ADPEDF) in Neovascular Age-Related Degeneration (AMD).* Sponsor: GenVec, Inc.

NIH/OBA Receipt Date: 7-11-01. Publicly Reviewed at the September 2001 RAC meeting.

0107-488 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Infectious Diseases/Human Immunodeficiency Virus/Replication Inhibition/Antisense/In Vitro/CD4+ Autologous Peripheral Blood Cells/Lentivirus/HIV-1/Antisense env/Intravenous

MacGregor, Rob Roy, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; *A Phase I Open-Label Clinical Trial of the Safety and Tolerability of Single Escalating Doses of Autologous CD4 T Cells Transduced with VRX496 in HIV Positive Subjects.* Sponsor: VIRxSYS Corporation.

NIH/OBA Receipt Date: 7-12-01. Publicly Reviewed at the September 2001 RAC meeting.

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0107-489 (Open) Gene Therapy/Phase I/Other/Restenosis In Vivo/Plasmid DNA/Vascular Endothelial Growth Factor cDNA/Intraarterial/Angioplasty Catheter

Losordo, Douglas W., St. Elizabeth's Medical Center, Boston, Massachusetts; *VEGF Gene Transfer to Prevent Coronary Artery Restenosis.*

NIH/OBA Receipt Date: 7-12-01. Not Selected for RAC Public Review: 7-31-01

0107-490 (Open) Gene Therapy/Phase I-II/Cancer/Melanoma/Immunotherapy/In Vivo/Naked Plasmid/Melan-A/MART-1/Intralymphnodal Injection

Weber, Jeffrey S., University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California; Hersh, Evan M., Arizona Cancer Center, Tucson, Arizona; Smith II, John W., Providence Portland Medical Center, Portland, Oregon; and Lerner, Adam, Boston University School of Medicine, Boston, Massachusetts; *A Pilot Phase I/II Study of Intranodal Delivery of a Plasmid DNA (Synchrovax SEM Vaccine) in Stage IV Melanoma Patients.* Sponsor: CTL ImmunoTherapies Corp.

NIH/OBA Receipt Date: 7-19-01. Not Selected for RAC Public Review: 8-8-01.

0107-491 (Open) Gene Therapy/Phase I/Cancer/Follicular Non-Hodgkin's Lymphoma/Immunotherapy/In Vitro/ Autologous T Lymphocytes/Plasmid DNA/Electroporation/CE7R-Specific scFvFc-Zeta T Cell Receptor/Intravenous Infusion

Press, Oliver W., University of Washington Medical Center, Seattle Washington; *A Phase I Study to Evaluate the Safety of Cellular Immunotherapy Using Genetically-Modified Autologous CD20-Specific CD8+ T Cell Clones for Patients with Relapsed CD20+ Indolent Lymphomas.*

NIH/OBA Receipt Date: 7-26-01. Not Selected for RAC Public Review: 8-15-01

0107-492 (Withdrawn-replaced by protocol # 0110-499) Gene Therapy/Phase I/Cancer/Liver (Hepatic) Metastases/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Sung, Max W., Mount Sinai Medical Center, New York, New York; *Clinical Trial of Adenoviral Vector Delivery of the Herpes Thymidine Kinase (HSV-TK) Gene by Intratumoral Injection Followed by Intravenous Ganciclovir with Imaging of HSV1-tk Gene Expression in Patients with Hepatic Metastases from Colorectal Cancer.*

NIH/OBA Receipt Date: 7-27-01.

0107-493 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Adeno-Associated Virus/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Subcutaneous Injection

Corman, John M., Virginia Mason Medical Center, Seattle, Washington; Simons, Jonathan, Emory University, Atlanta, Georgia; Small, Eric, University of California, San Francisco, San Francisco, California; Higano, Celestia, University of Washington, Seattle, Washington; Smith, David, University of Michigan Medical Center, Ann Arbor, Michigan; and Hudes, Gary R., Fox Chase Cancer Center, Philadelphia, Pennsylvania; *A Phase I/II Dose Escalation and Efficacy Trial of GVAX® Prostate Cancer Vaccine in Patients with Metastatic Hormone-Refractory Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 7-18-01. Not Selected for RAC Public Review: 8-31-01

0108-494 (Open) Gene Therapy/Monogenic Disease/X-Linked Severe Combined Immune Deficiency/In Vitro/Autologous CD34+ Cells from Cord Blood or Bone Marrow/Retroviral Vector/γc cDNA/Intravenous Infusion

Weinberg, Kenneth I., Children's Hospital of Los Angeles, University of Southern California School of Medicine, Los Angeles, California; *Gene Transfer of the γ cDNA into CD34+ Hematopoietic Cells of Infants or Children with X-Linked Severe Combined Immune Deficiency (X-SCID).*

NIH/OBA Receipt Date: 8-27-01. Not Selected for RAC Public Review: 9-17-01

0108-495 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy/In Vivo/Vaccinia Virus/DF3/MUC1/B7.1 (CD 80)/ICAM-1/LFA-3/Intradermal Injection

Eder, Joseph Paul, Dana-Farber Cancer Institute, Boston, Massachusetts; *A Phase I Trial of Recombinant Vaccinia Viruses that Express DF3/MUC1 and TRICOM (B7.1, ICAM-1, and LFA-3) in Patients with Metastatic Adenocarcinoma of the Breast.*

NIH/OBA Receipt Date: 8-27-01. Not Selected for RAC Public Review: 3-6-02

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0108-496 (Open) Gene Therapy/Phase I/Cancer/Malignant Glioma/Immunotherapy/In Vitro/Autologous T Lymphocytes/Plasmid DNA/Electroporation/IL13R α 2-Specific scFvFc-Zeta T Cell Receptor/Intracavity Administration

Jensen, Michael, City of Hope National Medical Center, Duarte, California; *Pilot Feasibility and Safety Study of Cellular Immunotherapy for Recurrent/Refractory Malignant Glioma using Genetically Modified Autologous CD8+ T Cell Clones.*

NIH/OBA Receipt Date: 8-30-01. Not Selected for RAC Public Review: 9-21-01

0109-497 (Open) Gene Therapy/Phase II/Cancer/MUC-1 Expressing Prostate Cancer/Immunotherapy/In Vivo/Vaccinia Virus/MUC-1/Interleukin-2/Subcutaneous Injection

Pantuck, Allan J., University of California, Los Angeles, Los Angeles, California; Dreicer, Robert, Cleveland Clinic Foundation, Cleveland, Ohio; Conlon, Kevin, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; Sahasrabudhe, Deepak, University of Rochester Medical Center, Rochester, New York; Higano, Celestia, Seattle Cancer Care Alliance, Seattle, Washington; Ahmann, Frederick, University of Arizona Cancer Center, Tucson, Arizona; and Stadler, Walter, University of Chicago, Chicago, Illinois; *Randomized Multicenter Phase II Study Evaluating Two Dosing Schedules of TG4010 (MVA-MUC1-IL2) in Patients with Adenocarcinoma of the Prostate.* Sponsor: Transgene, Inc.

NIH/OBA Receipt Date: 9-12-01. Not Selected for RAC Public Review: 10-9-01

0109-498 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfusion/Human Telomerase Reverse Transcriptase (hTERT)/Intradermal Injections

Vieweg, Johannes, Duke University Medical Center, Durham, North Carolina; *Phase I Study of Active Immunotherapy of Metastatic, Hormone Refractory Prostate Carcinoma using Autologous Mature Dendritic Cells (DC) Transfected with RNA Encoding Human Telomerase Reverse Transcriptase (hTERT).*

NIH/OBA Receipt Date: 9-21-01. Not Selected for RAC Public Review: 10-26-01

0110-499 (Open) Gene Therapy/Phase I/Cancer/Liver (Hepatic) Metastases of Colorectal Cancer/Pro-Drug/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase Gene/Ganciclovir/Intratumoral Injection

Sung, Max W., Mount Sinai Medical Center, New York, New York; *Clinical Trial of Adenoviral Vector Delivery of the Herpes Thymidine Kinase (HSV-tk) Gene by Intratumoral Injection Followed by Intravenous Ganciclovir with Imaging of HSV-tk Gene Expression in Patients with Hepatic Metastases from Colorectal Cancer.*

NIH/OBA Receipt Date: 10-9-01. Not Selected for RAC Public Review: 10-30-01

0110-500 (Open) Gene Therapy/Phase I/Cancer/Bladder/Pro-Drug/Ganciclovir/In Vivo/Adenovirus/Herpes Simplex Thymidine Kinase cDNA/Intratumoral Injection

Lerner, Seth P., Baylor College of Medicine, Houston, Texas; *Phase I Trial of Adenoviral Mediated Suicide Gene Therapy with HSV-tk Followed by Intravenous Administration of Ganciclovir in Patients with Locally Advanced and Refractory Superficial Bladder Cancer.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

0110-501 (Open) Gene Marking/Osteogenesis Imperfecta/In Vitro/CD34+ Cells from Donor Bone Marrow/Retrovirus/Neomycin Phosphotransferase cDNA/Intravenous Infusion

Horwotz, Edwin M., St. Jude Children's Research Hospital, Memphis, Tennessee; *Treatment of Children with Severe Osteogenesis Imperfecta by Stem Cell Transplantation and Mesenchymal Cell Graft Augmentation (Pilot Study).*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

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0110-502 (Open) Gene Therapy/Phase II/Peripheral Artery Disease/Plasmid DNA/Fibroblast Growth Factor 1 cDNA/Intramuscular Injection

Comerota, Anthony J., Temple University School of Medicine, Philadelphia, Pennsylvania; Mendelsohn, Farrell O., Cardiology, P.C., Birmingham, Alabama; Saucedo, Jorge F., University of Arkansas for Medical Sciences, Little Rock, Arkansas; Goldman, Corey K, Watson Clinic LLP, Lakeland, Florida; Greenbaum, Adam, Henry Ford Hospital, Detroit, Michigan; Sequeira, Rafael, Jackson Memorial Hospital, Miami, Florida; Henry, Timothy, Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; Miller, Julie, The Johns Hopkins University, Baltimore, Maryland; Gray, John, Durham VA Medical Center, Durham, North Carolina; Hermiller, James and Irwin, Randy, St. Vincent Hospital and Health Care Center, Indianapolis, Indiana; Moneta, Gregory, Oregon Health & Science University, Portland, Oregon; Laird, John, Washington Hospital Center, Washington, DC; Chronos, Nicolas, Atlanta Cardiology Group, Atlanta, Georgia; Kent, K. Craig, Weill Medical College of Cornell University, New York, New York; Grossman, P. Michael, The University of Michigan Health Systems, Ann Arbor, Michigan; and Eslami, Mohammad, Temple University, Philadelphia, Pennsylvania; *A Phase II, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Efficacy and Safety Study of Different Doses and Schedules of Administration of NV1FGF in Patients with Severe Peripheral Artery Occlusive Disease.* Sponsor: Aventis Pharma.

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 11-15-01

0110-503 (Open) Gene Therapy/Phase I/Monogenic Disease/Cystic Fibrosis/In Vivo/Nasal Epithelial Cells/Cystic Fibrosis Transmembrane Conductance Regulator cDNA/Polylysine Polyethylene Glycol Complex/Intranasal Administration

Konstan, Michael W., Case Western Reserve University, Cleveland, Ohio; and Wagener, Jeffrey, University of Colorado School of Medicine, Denver, Colorado; *Single Dose Escalation Study to Evaluate Safety of Nasal Administration of CFTR001 Gene Transfer Vector to Subjects with Cystic Fibrosis.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

0110-504 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vitro/Autologous T Lymphocytes/Retrovirus/T Cell Receptor α and β Chain cDNA/Intravenous Infusion

McDonagh, Kevin T., The University of Michigan Health System, Ann Arbor, Michigan; *A Phase I Study of Genetically Modified Autologous Peripheral Blood T-Cells Expressing a Retrovirally Encoded, MART-1 Specific αβ T-Cell Receptor, With and Without Recombinant Human Interleukin-2, in HLA-A2+.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

0110-505 (Open) Gene Therapy/Phase I/Cancer/MUC1 Expressing Carcinoma/Immunotherapy/In Vivo/Naked Plasmid DNA/MUC-1/Intramuscular Injection

Avigan, David E., Beth Israel Deaconess Medical Center, Boston, Massachusetts; *A Phase I Open-Label Study to Assess the Safety and Toxicity of Plasmid DNA MUC1 Vaccine (pMC6.5) in Metastatic Carcinoma.* Sponsor: Centocor, Inc.

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 11-12-01

0110-506 (Open) Gene Therapy/Phase I/Cancer/Melanoma/In Vitro/autologous T-Lymphocytes/Immunotherapy/Retrovirus/Interleukin-2 cDNA/Intravenous or Intra-arterial Infusion

Rosenberg, Steven A., National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Metastatic Melanoma using Lymphocytes Transduced with an Interleukin-2 (IL-2) Gene Following the Administration of a Nonmyeloablative but Lymphocyte Depleting Regimen.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 11-14-01

0110-507 (Open) Gene Therapy/Phase I/Cancer/Melanoma/Immunotherapy/In Vivo/Plasmid DNA/Granulocyte-Macrophage Colony Stimulating Factor cDNA/Intradermal Injection

Wolchok, Jedd D., Memorial Sloan-Kettering Cancer Center, New York, New York; *Vaccination of AJCC Stage IIB, IIC, III and IV Melanoma Patients with a Multi-Epitope Peptide Vaccine using GM-CSF DNA as an Adjuvant: A Pilot Trial to Assess Safety and Immunity.*

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

0110-508 (Open) Gene Therapy/Phase I/Infectious Disease/Human Immunodeficiency Virus/Replication Inhibition/Antisense/Antisense TAR/Antisense tat/rev/In Vitro/CD34+ Cells/Intravenous

Krishnan, Amrita, City of Hope National Medical Center, Duarte, California; *Evaluation of the Safety and Efficacy of ex vivo Modification and Re-Infusion of CD34+ Cells by an Antisense Construct against HIV-1 in a Retrovirus Vector.* Sponsor: Enzo Therapeutics, Inc.

NIH/OBA Receipt Date: 10-10-01. Not Selected for RAC Public Review: 10-30-01

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0111-509 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Vector Directed Cell Lysis/In Vivo/Adenovirus/Serotype 5/Replication-Comptetent Virus/Promoter and Enhancer Elements of the Prostate Specific Antigen Gene/Intratumoral Injection

Corman, John M., Virginia Mason Medical Center, Seattle Washington; *A Phase I/II Trial of Intraprostatic Injection of CG7060 Followed by Three-Dimensional Conformal Radiation Therapy (3D-CRT) in Patients with Clinically Localized Intermediate or High-Risk Prostate Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 11-9-01. Not Selected for RAC Public Review: 12-03-01

0111-510 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Prostate Specific Antigen/Intradermal Injection

Vieweg, Johannes, Duke University Medical Center, Durham, North Carolina; *Pilot Study evaluating the Migratory Patterns of Immature and In Vitro Matured Dendritic Cells Transfected with RNA Encoding PSA in Patients with Metastatic Prostate Cancer.*

NIH/OBA Receipt Date: 11-20-01. Not Selected for RAC Public Review: 12-11-01

0112-511 (Open) Gene Therapy/Phase I/Cancer Squamous Cell Carcinoma of the Head and Neck (SCCHN)/Immunotherapy/In Vitro/Allogeneic Tumor Cell/Retrovirus/Interleukin-2 cDNA/Intradermal Injection

Johnson, Jonas T., University of Pittsburgh, Pittsburgh, Pennsylvania; *Active Immunization of Patients with Carcinoma of Oral Cavity or Oropharynx with Interleukin-2-Secreting Semi-allogeneic Human Carcinoma Cell Line Transfected with DNA from Autologous Tumor (Phase I Study).*

NIH/OBA Receipt Date: 12-20-01. Not Selected for RAC Public Review: 1-14-02

0112-512 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Cachexia/In Vivo/Plasmid/Chimeric Transactivator of Progesterone Receptor-Ligand-Binding Domain Fused to the Gal4 DNA Binding Domain/Human Growth Hormone Releasing Hormone (GHRH) cDNA/Intramuscular Injection

Popat, Uday, Baylor College of Medicine, Houston, Texas; *Phase I Study of Human Growth Hormone Releasing Hormone Expressed by a Plasmid DNA Myogenic Vector in Patients with Cancer Cachexia.*

NIH/OBA Receipt Date: 12-21-01. Publicly Reviewed at the March 2002 RAC meeting

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0201-513 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer (NSCLC)/In Vivo/Tumor Suppressor Gene/Cationic Liposome Complex/DOTAP:Cholesterol/Fus 1 cDNA/Intravenous Injection

Lu, Charles, The University of Texas, MD Anderson Cancer Center, Houston, Texas; *Phase I Study of Intravenous DOTAP:Cholesterol-Fus 1 Liposome Complex (DOTAP:Chol-Fus 1) in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Previously Treated with Chemotherapy.*

NIH/OBA Receipt Date: 01-08-02. Publicly Reviewed at the March 2002 RAC meeting

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0201-514 (RAC Reviewed with Recommendations) Gene Marking/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Serotype 2/Human Placental Alkaline Phosphatase (AP or hpAP) cDNA/Nasal and Bronchial Administration

Aitken, Moira L., and Miller, A. Dusty, University of Washington, Seattle, Washington; *Transduction of the Upper and Lower Airway Epithelium in Health Subjects by an AAV2 Vector that Encodes Human Placental Alkaline Phosphatase.*

NIH/OBA Receipt Date: 01-09-02. Publicly Reviewed at the March 2002 RAC meeting

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0201-515 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Glioblastoma Multiforme/In Vivo/Herpes Simplex Virus Type 1/HSV Thymidine Kinase (TK), Connexin 43, Tumor Necrosis Factor Alpha (TNF-a), and the Viral Infected Cell Protein Zero (ICP0) Genes/Ganciclovir/Intratumoral (Stereotactic) Injections

Lunsford, L. Dade, and Glorioso, Joseph C., University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania; *Gene Therapy of Progressive Glioblastoma Multiforme using a Replication Defective HSV Multigene Vector NUREL-C2: A Phase I Clinical Trial to Determine the Maximum Tolerable Dose of Vector in Combination with Ganciclovir and Radiosurgery.*

NIH/OBA Receipt Date: 01-09-02. Publicly Reviewed at the March 2002 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0201-516 (Open) Gene Therapy/Phase I-II/Monogenic Disease/X-Linked Severe Combined Immune Deficiency/In Vitro/Autologous CD34+ Cells from Peripheral Blood/Retrovirus γcDNA/Intravenous Infusion

Malech, Harry L., National Institutes of Health, Bethesda, Maryland; *Ex Vivo Retroviral Gene Transfer for Treatment of X-Linked Severe Combined Immunodeficiency (XSCID).*

NIH/OBA Receipt Date: 1-15-02. Not Selected for RAC Public Review: 2-5-02

0203-517 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Human Interferon-beta cDNA/Intratumoral Injection

Dinney, Colin P., University of Texas MD Anderson Cancer Center; *An Open Label, Dose-Escalation Study to Determine the Tolerability of Interferon-beta (BG00001) Gene Transfer in the Neoadjuvant Treatment of High-Risk Resectable Prostate Cancer.* Sponsor: Biogen, Inc.

NIH/OBA Receipt Date: 3-5-02. Not Selected for RAC Public Review: 3-25-02

0203-518 (Submission Not Complete) Gene Therapy/Phase II/Cancer/Prostate/Immunotherapy/In Vivo/Fowlpox Virus/Prostate Specific Antigen/Intradermal Injection

Phase II Randomized Study of Fowlpox PSA Vaccine with and without GM-CSF in the Treatment of Advanced Prostate Cancer. Sponsor: Eastern Cooperative Oncology Group

NIH/OBA Receipt Date: 3-11-02.

0203-519 (Open) Gene Therapy/Phase II/Cancer/Pancreas/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Plasmid/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Intradermal Injection

Laheru, Daniel, John Hopkins University School of Medicine, Baltimore, Maryland; *A Phase II Trial of CG8020 and CG2505 in Patients with Nonresectable or Metastatic Pancreatic Cancer.* Sponsor: Cell Genesys, Inc.

NIH/OBA Receipt Date: 3-15-02. Not Selected for RAC Public Review: 4-4-02

0203-520 (Open) Gene Therapy/Phase I/Monogenic Disease/Fanconi Anemia/Pro-Drug/Ganciclovir/In Vitro/Allogeneic T Lymphocytes/Retrovirus/Herpes Simplex Thymidine Kinase cDNA/Graft-Versus-Host Disease/Intravenous Infusion

Orchard, Paul J., University of Minnesota Medical School, Minneapolis, Minnesota; *Transplantation of Unrelated or Mismatched Related Donor T Cells Containing the HSV-TK Suicide Gene to Facilitate Engraftment and Control Graft-Versus-Host Disease in Patients with Fanconi Anemia. A Phase I Trial.*

NIH/OBA Receipt Date: 3-21-02. Not Selected for RAC Public Review: 6-21-02

0204-521 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/End Stage Renal Disease/Stenosis Prevention/In Vivo/Adenovirus/Inducible Nitric Oxide Synthase (iNOS) cDNA/Administration at the Arteriovenous (AV) Graft for Hemodialysis Access

Tzeng, Elizabeth, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; *Inducible Nitric Oxide Synthase Gene Therapy for the Prevention of Intimal Hyperplasia in Arteriovenous Grafts used for Hemodialysis Access.*

NIH/OBA Receipt Date: 4-1-02. Publicly Reviewed at the June 2002 RAC meeting

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0204-522 (Open) Gene Therapy/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen cDNA/B7.1 (CD80) cDNA/Intramuscular or Intradermal Injection

Dahut, William, National Institutes of Health, Bethesda, Maryland; *A Pilot Trial of Concurrent Docetaxel and Pox Vector PSA Vaccine Followed by Docetaxel in Metastatic Androgen Independent Prostate Cancer.*

NIH/OBA Receipt Date: 4-9-02. Not Selected for RAC Public Review: 4-29-02

0204-523 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Ovarian/Immunotherapy/In Vivo/Measles Virus/Carcinoembryonic Antigen (CEA) cDNA/Intraperitoneal Administration

Galanis, Evanthia, Mayo Clinic, Rochester, Minnesota; *Phase I Trial of Intraperitoneal Administration of an Attenuated Strain (Edmonston Strain) of Measles Virus, Genetically Engineered to Produce CEA, in Patients with Recurrent Ovarian Cancer.*

NIH/OBA Receipt Date: 4-11-02. Publicly Reviewed at the June 2002 RAC meeting

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0204-524 (Open) Gene Therapy/Phase I/Cancer/Breast/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD80)/ICAM-1/LFA-3/Intramuscular or Intradermal Injection

Arlen, Philip M., National Institutes of Health, Bethesda, Maryland; *A Pilot Study of Sequential Vaccinations with Recombinant Vaccinia-CEA(6D)-TRICOM, and Recombinant Fowlpox-CEA(6D)-TRICOM (B7.1/ICAM-1/LFA-3) with Sargramostim (GM-CSF) , in Conjunction with Standard Adjuvant Chemotherapy in High Risk Breast Cancer Patients Status Post Surgery with 4+ or More Lymph Nodes and CEA Expressing Tumors*

NIH/OBA Receipt Date: 4-16-02. Not Selected for RAC Public Review: 5-6-02

0204-525 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Oncogene-Regulation/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intraperitoneal Administration

Wolf, Judith K., The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I Dose Escalation Study of Intraperitoneal tgDCC-E1A and Intravenous Carboplatin for Treatment of Recurrent, Platinum-Sensitive Ovarian Cancer.* Sponsor: Targeted Genetics Corp.

NIH/OBA Receipt Date: 4-24-02. Not Selected for RAC Public Review: 5-14-02

0204-526 (Open) Gene Therapy/Phase I/Cancer/Colon Carcinoma (Hepatic Metastasis)/Herpes Simplex Virus Type-1/Tumor Lysis/Intrahepatic Artery Administration

Fong, Yuman, Memorial Sloan-Kettering Cancer Center, New York, New York; *A Phase I, Open-Label, Dose-Escalating Study of Safety, Tolerability, and Anti-Tumor Activity of a Single Intrahepatic Arterial Injection of a Genetically Engineered Herpes Simplex Virus, NV1020, in Herpes Simplex Seronegative Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 4-23-02. Not Selected for RAC Public Review: 5-13-02

0204-527 (Open) Gene Therapy/Phase I/Cancer/Colon Carcinoma (Hepatic Metastasis)/Herpes Simplex Virus Type-1/Tumor Lysis/Intrahepatic Artery Administration

Fong, Yuman, Memorial Sloan-Kettering Cancer Center, New York, New York; *Long-Term Follow-Up of the Safety and Survival of HSV Simplex Seronegative Subjects with Adenocarcinoma of the Colon with Metastasis to the Liver Who Enrolled in a Phase I Dose-Escalating Study Evaluating Genetically Engineered Herpes Simplex Virus, NV1020.* Sponsor: MediGene, Inc.

NIH/OBA Receipt Date: 4-23-02. Not Selected for RAC Public Review: 5-13-02

0204-528 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Other Disorders/Erectile Dysfunction/In Vivo/Plasmid/Human Maxi-K Channel hSlo cDNA/Intracavernous Injection

Melman, Arnold, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York; *Pilot Study of the Human hslo/maxi-K Gene to Treat Erectile Dysfunction.*

NIH/OBA Receipt Date: 4-23-02. Publicly Reviewed at the June 2002 RAC meeting

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0204-529 (RAC Reviewed with Recommendations) Gene Therapy/Other Disorders/Intractable Pain/In Vivo/Herpes Simplex Virus Type 1/Proenkephalin/Subcutaneous Inoculation

Fink, David, and Glorioso, Joseph, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; *Gene Transfer for Intractable Pain: A Phase I Clinical Trial to Determine the Maximum Tolerable Dose of a Replication Defective HSV Vector Expressing Human Proenkephalin.*

NIH/OBA Receipt Date: 4-24-02. Publicly Reviewed at the June 2002 RAC meeting

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0204-530 (Open) Gene Therapy/Phase II/Cancer/Pancreatic Cancer/Immunotherapy/In Vivo/Adenovirus/Type 5/Tumor Necrosis Factor cDNA/Intratumoral Injection

Senzer, Neil Nathan, U.S. Oncology, Inc., Dallas Texas; Richards, Donald, Tyler Care Center, Tyler, Texas; Hecht, J. Randolph, UCLA Medical Center, Los Angeles , California; Hanna, Nader, University of Kentucky, Lexington, Kentucky; Chung, Theodore D.K., Virginia Commonwealth University, Richmond, Virginia; Vogel, Stephen, The University of Florida, Gainesville, Florida; Reid, Tony, Palo Alto VA Health Care Systems, Palo Alto, California; Chang, Kenneth J., University of California, Irvine, Orange, California; Javle, Milind, Roswell Park Cancer Institute, Buffalo, New York; Erickson, Richard, Scott & White Memorial Hospital and Clinic, Temple, Texas; and Rosemurgy, Alexander, University of South Florida, Tampa, Florida; *A Randomized, Phase II, Study of TNFerade™ Biologic with 5-FU and Radiation Therapy for First-Line Treatment of Unresectable Locally Advanced Pancreatic Cancer.* Sponsor: GenVec, Inc.

NIH/OBA Receipt Date: 4-24-02. Not Selected for RAC Public Review: 5-14-02

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0204-531 (Open) Gene Therapy/Cancer/Mesothelioma/Immunotherapy/In Vivo/Adenovirus/Serotype 5/Interferon-beta/Intrapleural Administration

Sterman, Daniel, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; *A Phase I Trial of Intrapleural Gene Therapy of Malignant Pleural Disease Using E1-Deleted Adenoviruses Containing the Human Interferon Beta Gene.*

NIH/OBA Receipt Date: 4-24-02. Not Selected for RAC Public Review: 5-14-02

0204-532 (Closed) Gene Therapy/Other Disorders/Peripheral Arterial Occlusive Disease (PAOD)/In Vivo/Adenovirus/Serotype 5/Fibroblast Growth Factor (FGF) cDNA/Intramuscular Injection

Haser, Paul B., St. Michael's Medical Center, Newark, New Jersey; *Double-Blind, Randomized, Placebo-Controlled Study of Ascending Doses on Tolerability of Ad5.1 Mediated Human FGF-4 Gene Transfer Given Intramuscularly on One Day in Patients with Peripheral Arterial Occlusive Disease (PAOD) Fontaine Stage III or Fontaine Stage IV.* Sponsor: Berlex Laboratories.

NIH/OBA Receipt Date: 4-24-02. Not Selected for RAC Public Review: 7-10-02
Closed: 12-16-02

0204-533 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Prostate/Radiotherapy/In Vivo/Adenovirus/Serotype 5/Human Sodium-Iodide Symporter (NIS) cDNA/Intratumoral Injection

Morris, John C., Mayo Clinic, Rochester, Minnesota; *Phase I Trial of In Situ Gene Therapy for Locally Recurrent Prostate Cancer Following Radiation Therapy Failure Using Sodium/Iodide Symporter and Radioiodine.*

NIH/OBA Receipt Date: 4-25-02. Publicly Reviewed at the June 2002 RAC meeting

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0204-534 (RAC Reviewed with Recommendations) Non-therapeutic (Healthy Volunteers)/Phase I/In Vivo/Adenovirus/Serotype 4/Human Immunodeficiency Virus-1 env Plus rev or gag/Protease Plus rev Inserted Genes/Oral or Intranasal Administration

Connors, Mark, National Institutes of Health, Bethesda, Maryland; *Phase I Study of AD4-ΔE3-HIV$_{env}$ and AD4-ΔE3-HIV$_{gag/pro}$ Recombinant Vaccines in HIV-negative Volunteers.*

NIH/OBA Receipt Date: 4-24-02. Publicly Reviewed at the June 2002 RAC meeting

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0205-535 (Open) Gene Therapy/Phase I/Cancer/Acute Lymphoblastic Leukemia (ALL)/Immunotherapy/In Vitro/Plasmid DNA/Chimeric T Cell Receptor (CD19R) cDNA/Fusion Gene Encoding Hygromycin Phosphotransferase and Herpes Simplex Thymidine Kinase (HyTK)/Intravenous Infusion

Cooper, Laurence J. N., City of Hope Medical Center, Duarte, California; *Phase I Study to Evaluate the Safety of Cellular Immunotherapy for High-Risk CD19+ Acute Lymphoblastic Leukemia after Autologous Hematopoietic Stem Cell Transplantation using Genetically Modified CD19-redirected Autologous Cytolytic T Cell Clones.*

NIH/OBA Receipt Date: 5-6-02. Not Selected for RAC Public Review: 5-28-02

0205-536 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen (PSA)/B7.1 (CD80)/ICAM-1/LFA-3/Subcutaneous Injection

Kaufman, Howard L., Columbia University, New York, New York; Plante, Mark, The University of Vermont, Burlington, Vermont; and DiPaola, Robert, Robert Wood Johnson Medical School, New Brunswick, New Jersey; *Phase I Open Label Study to Evaluate the Safety of PROSTVAC-VF-TRICOM in the Treatment of Subjects with Adenocarcinoma of the Prostate.* Sponsor: Therion Biologics Corporation.

NIH/OBA Receipt Date: 5-16-02. Not Selected for RAC Public Review: 6-26-02

0205-537 (Open) Gene Therapy/Phase I-II/Cancer/Breast/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD80)/ICAM-1/LFA-3/Intramuscular Or Intradermal Injection

Kasten-Sportes, Claude, National Institutes of Health, Bethesda, Maryland; *A Phase I-II Study of Tumor Antigen (CEA) Immunization with Autologous Peripheral Progenitor Cell Transplantation in Patients Previously Untreated for Metastatic Breast Cancer.*

NIH/OBA Receipt Date: 5-24-02. Not Selected for RAC Public Review: 6-14-02

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0205-538 (Open) Gene Therapy/Phase I-II/Cancer/Small Cell Lung Cancer/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/p53 cDNA/Intradermal Injection

Antonia, Scott J., University of South Florida, Tampa, Florida; *A Phase I-II Trial Using Dendritic Cells Transduced with an Adenoviral Vector Containing the p53 Gene to Immunize Patients with Extensive Stage Small Cell Lung Cancer after Standard Chemotherapy.*

NIH/OBA Receipt Date: 5-24-02. Not Selected for RAC Public Review: 6-14-02

0206-539 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Other Disorders/Superficial Corneal Opacity/Corneal Scarring/InVivo/Retrovirus/dnG1 Cyclin/Eye Administration (Ophthalmic Instillation)

Song, Jonathan C., Keck School of Medicine, University of Southern California, Los Angeles, California; *Phase I/II Evaluation of Safety and Efficacy of a Matrix-Targeted Retroviral Vector Bearing a Dominant Negative Cyclin G1 Construct (Mx-dnG1) as Adjunctive Intervention for Superficial Corneal Opacity/Corneal Scarring.*

NIH/OBA Receipt Date: 6-5-02. Publicly Reviewed at the September 2002 RAC meeting

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0206-540 (Open) Gene Therapy/Phase I/Cancer/Ovarian/Oncogene-Regulation/In Vivo/Cationic Liposome Complex/DC-Chol-DOPE/E1A/Intraperitoneal Administration

Wolf, Judith K., The University of Texas MD Anderson Cancer Center, Houston, Texas; *A Phase I Dose Escalation Study of Intraperitoneal tgDCC-E1A and Intravenous Paclitaxel in Women with Platinum-Resistant Ovarian Cancer.* Sponsor: Targeted Genetics Corp.

NIH/OBA Receipt Date: 6-6-02. Not Selected for RAC Public Review: 6-26-02

0206-541 (Open) Gene Therapy/Phase I-II/Cancer/Breast/Immunotherapy/In Vivo/Naked Plasmid/Gene Encoding NY-ESO-1 Epitope/Intralymphnodal Injection

Waisman, James R., University of Southern California, Los Angeles, California; *A Phase I/II Study of Intranodal Delivery of Synchrovax BPL Vaccine, an Epitope Synchronization Plasmid DNA Vaccine, in Sage IV Breast Carcinoma Patients.* Sponsor: CTL ImmunoTherapies Corporation.

NIH/OBA Receipt Date: 6-13-02. Not Selected for RAC Public Review: 7-18-02

0207-542 (Open) Gene Therapy/Phase I-II/Cancer/Pancreas/Pro-Drug/Valacyclovir/In Vivo/Adenovirus/Serotype 5/Herpes Simplex Thymidine Kinase cDNA/Intratumoral Injection

Fernandez-del Castillo, Carlo, Massachusetts General Hospital, Boston, Massachusetts; and Aguilar-Cordova, Estuardo, Harvard Gene Therapy Initiative, Boston, Massachusetts; *AdV-tk Gene Therapy in Combination with Chemoradiation for Locally Advanced Pancreatic Cancer.*

NIH/OBA Receipt Date: 7-17-02. Not Selected for RAC Public Review: 8-6-02

0207-543 (Open) Gene Therapy/Phase I/Cancer/Follicular Lymphoma/Immunotherapy/In Vitro/Plasmid DNA/Chimeric T Cell Receptor (CD19R) cDNA/Fusion Gene Encoding Hygromycin Phosphotransferase and Herpes Simplex Virus Thymidine Kinase

Cooper, Laurence J. N., City of Hope National Medical Center, Duarte, California; *Phase I Study to Evaluate the Safety of Cellular Immunotherapy for CD 19+ Follicular Lymphoma Using Autologous T Cell Cytolytic Clones Genetically Modified to be CD19-Specific and Express HyTK.*

NIH/OBA Receipt Date: 7-18-02. Not Selected for RAC Public Review: 8-7-02

0207-544 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Melanoma/Pro-Drug/Valacyclovir/In Vivo/DNA-Liposome Complexes/Herpes Simplex Thymidine Kinase cDNA/Intravenous Injection

Thompson, John A., Seattle Cancer Care Alliance and The University of Washington, Seattle, Washington; *A Phase I Study to Evaluate the Safety and Pharmacokinetics of Pro-1, a Liposome-Encapsulated Thymidine Kinase Gene Formulation, in Patients with Stage IV Metastatic Melanoma.* Sponsor: Protiva Biotherapeutics, Inc.

NIH/OBA Receipt Date: 7-24-02. Publicly Reviewed at the September 2002 RAC meeting

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0207-545 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vitro/Autologous Peripheral Blood Lymphocytes/Plasmid DNA/Immunoglobulin Heavy (H) Chain Gene/Telomerase Reverse Transcriptase (hTERT) Gene/Intravenous Infusion

Zanetti, Maurizio, University of California, San Diego, San Diego, California; *A Phase I/II, Escalating Dose, Open Label Evaluation of Safety, Feasibility and Tolerability of Transgenic Lymphocyte Immunization Vaccine (TLI) in Subjects with Histologically Proven Prostate Adenocarcinoma.* Sponsor: Cosmo Bioscience, Inc.
NIH/OBA Receipt Date: 7-24-02. Publicly Reviewed at the September 2002 RAC meeting

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0207-546 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Peripheral Artery Disease/Plasmid DNA/Hepatocyte Growth Factor cDNA/Intramuscular Injection

Powell, Richard J., Dartmouth Medical School, Lebanon, New Hampshire; *A Phase I/II Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety and Efficacy of AMG0001 to Improve Perfusion in Critical Leg Ischemia.* Sponsor: AnGes, Inc.

NIH/OBA Receipt Date: 7-24-02. Publicly Reviewed at the September 2002 RAC meeting

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0207-547 (Withdrawn from RAC Review) Gene Therapy/Phase I-II/Peripheral Artery Disease/Plasmid DNA/Hepatocyte Growth Factor cDNA/Intramuscular Injection

Powell, Richard J., Dartmouth Medical School, Lebanon, New Hampshire; *A Phase I/II Double-Blind, Randomized, Placebo-Controlled Study to Assess the Safety and Efficacy of AMG0001 to Improve Perfusion and Healing After Major Amputation Due to Critical Leg Ischemia.* Sponsor: AnGes, Inc.

NIH/OBA Receipt Date: 7-24-02. Withdrawn from RAC review: 9-6-02.

0207-548 (Open) Gene Therapy/Phase I/Cancer/Renal Cell Carcinoma/Immunotherapy/In Vitro/Autologous Dendritic Cells/RNA Transfer/Total Tumor RNA/Intravenous Infusion

Vieweg, Johannes and Chao, Nelson, Duke University Medical Center, Durham, North Carolina; *Active Immunotherapy with Mature, Tumor RNA-Transfected, Autologous Dendritic Cells with or without the IL2-Diphtheria Toxin Conjugate Denileukin Difitox (Ontak®) in Patients with Metastatic Renal Cell Carcinoma.*

NIH/OBA Receipt Date: 7-29-02. Not Selected for RAC Public Review: 8-16-02

0208-549 (Open) Gene Therapy/Phase II/Cancer/Esophagus/Immunotherapy/In Vivo/Adenovirus/Type 5/Tumor Necrosis Factor cDNA/Intratumoral Injection

Senzer, Neil, US Oncology, Dallas, Texas; *A Phase II, Multi-Center, Single Arm Evaluation of Preoperative Chemoradiation Plus TNFerade™ Biologic (Ad_{GV}EGR.TNF.11D) Prior to Esophagectomy for Locally Advanced Esophageal Cancer.* Sponsor: GenVec.

NIH/OBA Receipt Date: 8-1-02. Not Selected for RAC Public Review: 8-21-02

0208-550 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Breast/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Retrovirus/α-(1,3) galactosyltransferase Gene/Subcutaneous Injection

Morton, Roscoe F., Iowa Methodist Medical Center, Des Moines, Iowa; *A Phase I/II Study of an Antitumor Vaccination Using α(1,3) galactosyltransferase Expressing Allogeneic Tumor Cells in Patients with Relapsed or Refractory Breast Cancer.* Sponsor: NewLink Genetics Corporation

NIH/OBA Receipt Date: 8-26-02. Publicly Reviewed at the December 2002 RAC meeting

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0210-551 (Open) Gene Therapy/Phase II/Cancer/Melanoma/Immunotherapy/In Vivo/Fowlpox Virus/Vaccinia Virus/Tyrosinase cDNA/Intramuscular Injection

Topalian, Suzanne, National Institutes of Health, Bethesda, Maryland; *Treatment of Patients with Metastatic Melanoma using Recombinant Vaccinia and Fowlpox Viruses Encoding the Tyrosinase Antigen in Combination with Interleukin-2.*

NIH/OBA Receipt Date: 10-3-02. Not Selected for RAC Public Review: 10-24-02

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0210-552 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Retrovirus/α(1, 3)galactosyltransferase Gene/Subcutaneous Injection

Morris, John C., National Institutes of Health, Bethesda, Maryland; *A Phase I/II Study of an Antitumor Vaccination using α(1, 3)galactosyltransferase Expressing Allogeneic Tumor Cells in Patients with Refractory or Recurrent Non-Small Cell Lung Cancer.* Sponsor: NewLink Genetics Corporation

NIH/OBA Receipt Date: 10-9-02. Publicly Reviewed at the December 2002 RAC meeting

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0210-553 (Open) Gene Therapy/Phase I/Cancer/Chronic Lymphocytic B-Leukemia/Immunotherapy/In Vitro/Plasmid DNA/Interleukin-2/CD40 Ligand/Subcutaneous Injections

Brenner, Malcolm, Baylor College of Medicine, Houston, Texas; *Treatment of Chronic Lymphocytic B-Leukemia (B-CLL) with Human IL-2 and Human CD40 Ligand Plasmid Gene Modified Autologous Tumor Cells.*

NIH/OBA Receipt Date: 10-9-02. Not Selected for RAC Public Review: 10-30-02

0210-554 (Open) Non-therapeutic (Healthy Volunteers)/Phase I/Infectious Diseases/Human Immunodeficiency Virus/In Vivo/Plasmid/HIV-1 Gag-Pol-Nef-Env cDNA/Interleukine-2 (IL-2)/Ig Fusion Protein/Bioinjector 2000® Injections

Dolin, Raphael, Harvard Medical School, Boston Massachusetts; Blattner, William, University of Maryland, Baltimore, Maryland; and Hammer, Scott Columbia University/New York Blood Center, New York, New York; *A Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of the HIV-1 DNA Vaccine VRC-HIVDNA009-00-VP (Gag-Pol-Nef-Multiclade Env) with the Plasmid Cytokine Adjuvant VRC-ADJDNA004-IL2-VP (IL-2/Ig).*

NIH/OBA Receipt Date: 10-9-02. Not Selected for RAC Public Review: 10-30-02

0210-555 (Open) Gene Therapy/Phase I/Cancer/Prostate/Immunotherapy/In Vivo/Plasmid/Prostate Specific Antigen (PSA)/Intramuscular Injection

Malkowicz, S. Bruce, University of Pennsylvania Health System, Philadelphia, Pennsylvania; *A Phase I Study of a Polynucleotide Anti-Tumor Immunization to Human Prostate Specific Antigen (PSA) in Patients with Hormone-Refractory Prostate Cancer (HRPC).* Sponsor: Centocor Inc.

NIH/OBA Receipt Date: 10-9-02. Not Selected for RAC Public Review: 10-30-02

0210-556 (RAC Reviewed with Recommendations) Gene Therapy/Phase I/Cancer/Non-Small Cell Lung Cancer/Immunotherapy/In Vivo/Plasmid DNA/Adenovirus/Serotype 5/L523S cDNA/Intramuscular Injection

Nemunaitis, John J., US Oncology, Dallas, Texas; *Phase I Open-Label, Dose Escalation Trial Evaluating the Safety and Immunogenicity of Sequential Administration of Recombinant DNA and Adenovirus Expressing L523S Protein in Patients with Early Stage Non-Small Cell Lung Cancer.* Sponsor: Corixa Corporation

NIH/OBA Receipt Date: 10-9-02. Publicly Reviewed at the December 2002 RAC meeting

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0210-557 (RAC Reviewed with Recommendations) Gene Therapy/Phase I-II/Coronary Artery Disease/Plasmid DNA/Hepatocyte Growth Factor cDNA/Intramyocardial Injection

Simons, Michael, Dartmouth Medical School, Lebanon, New Hampshire; and Annex, Brian H., Duke University School of Medicine, Durham VA Medical Center, Durham, North Carolina; *A Double-Blind, Placebo-Controlled, Dose Escalation Pilot Study to Assess the Safety and Effects of AMG0001 in Patients with Ischemic Heart Disease (IHD) not Amenable to Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI).* Sponsor: AnGes, Inc.

NIH/OBA Receipt Date: 10-9-02. Publicly Reviewed at the December 2002 RAC meeting

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0212-558 (Open) Gene Therapy/Phase I-II/Cancer/Breast/Immunotherapy/In Vitro/Autologous Dendritic Cells/Adenovirus/Serotype 5/p53 cDNA/Subcutaneous Injection

Reed, Elizabeth C., University of Nebraska Medical Center, Omaha, Nebraska; *Adenovirus p53 Infected DC Vaccine for Breast Cancer.*

NIH/OBA Receipt Date: 12-9-02. Not Selected for RAC Public Review: 1-13-03

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0212-559 (Open) Gene Therapy/Phase I/Cancer/Pancreas/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Carcinoembryonic Antigen (CEA)/B7.1 (CD80)/ICAM-1/LFA-3/MUC-1/Subcutaneous Injection

Kaufman, Howard L., Columbia University, New York, New York; *An Open Label Phase I Study to Evaluate the Safety and Tolerability of rV-CEA(6D)/TRICOM™ Admixed with rV-MUC-1 followed by rF-CE(6D)/TRICOM™ in Combination with GM-CSF in Subjects with Unresectable Adenocarcinoma of the Pancreas.* Sponsor: Therion Biologics Corporation.

NIH/OBA Receipt Date: 12-10-02. Not Selected for RAC Public Review: 1-06-03

0212-560 (Open) Gene Therapy/Phase I-II/Cancer/Prostate/Immunotherapy/In Vivo/Vaccinia Virus/Fowlpox Virus/Prostate Specific Antigen (PSA)/B7.1 (CD80)/ICAM-1/LFA-/GM-CSF/Intramuscular Or Intradermal Injection

Arlen, Philip M., National Institutes of Health, Bethesda, Maryland; *A Phase I/II Pilot Study of Sequential Vaccinations with rFOWLPOX-PSA (L155)-TRICOM (PROSTAVAC-F/TRICOM) Alone, or in Combination with rVACCINIA-PSA (L155)-TRICOM (PROSTAVAC-V/TRICOM) and the Role of GM-CSF, in Patients with Prostate Cancer.* Sponsor: Therion Biologics Corporation.

NIH/OBA Receipt Date: 12-10-02. Not Selected for RAC Public Review: 1-06-03

0212-561 (Open) Gene Therapy/Phase I/Cancer/Pancreas/Immunotherapy/In Vitro/Allogeneic Tumor Cells/Lethally Irradiated/Plasmid/Cytokine/Granulocyte-Macrophage Colony Stimulating Factor/Intradermal Injection

Shuman, Marc, University of California, San Francisco Cancer Center, San Francisco, California; *Pancreatic GVAX® for Resected Adenocarcinoma of the Pancreas.*

NIH/OBA Receipt Date: 09-04-02. Not Selected for RAC Public Review: 1-03-03

0212-562 (Open) Gene Therapy/Phase I/Cancer/Immunotherapy/In Vitro/Allogeneic K562 Cell/Combination With Untransduced Tumor Cells/Plasmid DNA/Electroporation/DMRIE-Cholesterol/Granulocyte-macrophage Colony Stimulating Factor cDNA/CD40 Ligand cDNA/Intradermal Injection

Dessureault, Sophie, University of South Florida, Tampa, Florida; *A Phase I Trial Using a Universal GM-CSF-Producing and CD40L-Expressing Bystander Cell Line (GM.CD40L) in the Formulation of Autologous Tumor Cell-Based Vaccines for Cancer Patients with Stage IV Disease.*

NIH/OBA Receipt Date: 12-18-02. Not Selected for RAC Public Review: 1-10-03

0212-563 (Under Review) Gene Therapy/Phase I/Cancer/Neuroblastoma/Immunotherapy/In Vitro/Autologous T Lymphocytes/Retrovirus/GD-2 Specific scFvFc-Zeta T Cell Receptor/Intravenous Injections

Russell, Heidi, and Brenner, Malcolm, Baylor College of Medicine, Houston, Texas; *Administration of Peripheral Blood T-Cells and EBV Specific CTLs Transduced to Express GD-2 Specific Chimeric T Cell Receptors to Patients with Neuroblastoma.*

NIH/OBA Receipt Date: 12-24-02.

0301-564 (Under Review) Gene Therapy/Phase I/Cancer Adenocarcinoma Expressing Carcinoembryonic Antigen (CEA)/Immunotherapy/In Vitro/Autologous T Lymphocytes/Retrovirus/Anti-CEA-sFv-Zeta T Cell Receptor-CD28/Intravenous Infusion

Junghans, Richard, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; *Phase Ia/Ib Trial of 2nd Generation Designer T Cells in Adenocarinoma.*

NIH/OBA Receipt Date: 1-06-03.

0301-565 (Closed) Gene Therapy/Phase I/Anaplastic Thyroid Cancer/Tumor Suppressor Gene/In Vivo/Adenovirus/Serotype 5 p53 cDNA/Intratumoral Injections

Reid, William K., Vanderbilt-Ingram Oncology, Vanderbilt University Medical Center, Franklin, Tennessee; *Study to Evaluate the Overall Response and Safety of Biweekly Intratumoral Administration of RPR/INGN 201 in Anaplastic Thyroid Cancer.*

NIH/OBA Receipt Date: 1-06-03. Not Selected for RAC Public Review

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

0301-566 (Under Review) Gene Therapy/Phase I/Cancer/Hematologic Malignancy Following Allogeneic Bone Marrow Transplantation/Pro-drug/Elimination of Graft Versus Host Disease/In Vitro/Allogeneic T Cells/Retrovirus/CD34-Herpes Simplex Virus Thymidine Kinase cDNA/Gangiclovir/Intravenous

DiPersio, John, Washington University School of Medicine, St. Louis, Missouri; *Infusion of Genetically Modified T Cells: Tracking and Toxicity.*

NIH/OBA Receipt Date: 1-07-03.

0301-567 (Open) Gene Therapy/Phase II/Coronary Artery Disease/In Vivo/Ischemic Myocardium/Plasmid DNA/Vascular Endothelial Growth Factor (VEGF) cDNA/Percutaneous Cardiac Catheterization/Intra-myocardial Injection

Losordo, Douglas W., St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston Massachusetts; *A Multicenter, Randomized, Double-Blind, Dose Ranging Placebo Controlled Study Evaluating Defined Doses of Percutaneously Delivered pVGl.1 (VEGF2) (Placebo, 2, 200, or 2000 μg) in "No Option" Patients with Class III or IV Angina with an Option for Patients to Receive Active Treatment at Month 6 if they Experience a Treatment Failure.* Sponsor: Corautus Genetics, Inc. (formerly Vascular Genetics, Inc.)

NIH/OBA Receipt Date: 1-08-03. Not Selected for RAC Public Review: 1-29-03

0301-568 (Open) Gene Therapy/Phase II/Peripheral Artery Disease/In Vivo/DNA-Liposome Complexes/Poloxamer 188/Del-1 cDNA/Intramuscular Injection

Rajagopalan, Sanjay, University of Michigan, Ann Arbor, Michigan; *A Phase II Multi-Center, Double-Blind, Placebo-Controlled, Trial of VLTS-589 in Subjects with Intermittent Claudication Secondary to Peripheral Arterial Disease.* Sponsor: Valentis, Inc.

NIH/OBA Receipt Date: 1-08-03. Not Selected for RAC Public Review: 1-29-03

0301-569 (Open) Gene Therapy/Phase II/Monogenic Disease/Cystic Fibrosis/In Vivo/Adeno-Associated Virus/Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) cDNA/Aerosol Administration

Moss, Richard, Stanford University School of Medicine, Palo Alto, California; *A Multicenter, Double-Blind, Placebo-Controlled, Phase II Study of Aerosolized tgAAVCF for the Treatment of Cystic Fibrosis.* Sponsor: Targeted Genetics Corporation.

NIH/OBA Receipt Date: 1-08-03. Not Selected for RAC Public Review: 1-29-03

0301-570 (Under Review) Non-therapeutic (Healthy Volunteers/Cholera Vaccine/In Vivo/*Vibrio cholerae*/Oral Administration

Tacket, Carol O., Center for Vaccine Development, University of Maryland, Baltimore, Maryland; *Use of in vivo Expression Technology to Identify Virulence Factors and Protective Antigens of Vibrio cholerae 01.*

NIH/OBA Receipt Date: 1-08-03.

(Scroll down for Summary Table)

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*The term "RAC Recommends Approval" for any submission indicates that the RAC made a recommendation to the NIH Director for approval of that submission.

HUMAN GENE TRANSFER PROTOCOLS
(please see explanation of review levels below)

	Review Level 1	Review Level 2	Review Level 3	Review Level 4	Review Level 5	Review Level 6	Review Level 7	TOTAL
MARKING	23	2	5	0	0	10	1	41
THERAPY	83	5	92	5	11	255	61	512
NON-THERAPEUTIC	1	0	0	0	1	1	2	5
INFECTIOUS DISEASES	8	1	11	1	1	14	2	38
1. Human Immunodeficiency Virus	8	1	11	1	1	13	2	37
2. Epstein Barr Virus/Cytomegalovirus Disease	0	0	0	0	0	1	0	1
MONOGENIC DISEASES	20	1	9	0	1	15	11	57
1. Alpha-1-Antitrypsin Deficiency	1	0	0	0	0	1	0	2
2. Chronic Granulomatous Disease	1	0	1	0	0	1	0	3
3. Cystic Fibrosis	10	1	5	0	0	6	1	23
4. Familial Hypercholesterolemia	1	0	0	0	0	0	0	1
5. Fanconi Anemia	1	0	0	0	0	3	0	4
6. Gaucher Disease	3	0	0	0	0	0	0	3
7. Hunter Syndrome	1	0	0	0	0	0	0	1
8. Ornithine Transcarbamylase Deficiency	0	0	1	0	0	0	0	1
9. Purine Nucleoside Phosphorylase Deficiency	1	0	0	0	0	0	0	1
10. SCID	1	0	1	0	0	3	1	6
11. Leukocyte Adherence Deficiency	0	0	1	0	0	0	0	1
12. Canavan Disease	0	0	0	0	0	1	2	3
13. Hemophilia	0	0	0	0	0	0	5	5
14. Muscular Dystrophy	0	0	0	0	0	0	1	1
15. Amyotrophic Lateral Sclerosis	0	0	0	0	1	0	0	1
16. Junctional Epidermolysis Bullosa	0	0	0	0	0	0	1	1
OTHER DISEASES / DISORDERS	2	0	2	2	2	31	20	59
1. Peripheral Artery Disease	1	0	0	1	1	16	1	20
2. Rheumatoid Arthritis	1	0	0	0	0	0	1	2
3. Arterial Restenosis	0	0	1	0	0	1	1	3
4. Cubital Tunnel Syndrome	0	0	1	0	0	0	0	1
5. Coronary Artery Disease	0	0	0	1	0	13	5	19
6. Alzheimer's Disease	0	0	0	0	0	0	1	1
7. Ulcer	0	0	0	0	0	1	2	3
8. Bone Fracture	0	0	0	0	1	0	0	1
9. Renal Disease	0	0	0	0	0	0	3	3
10. Peripheral Neuropathy	0	0	0	0	0	0	1	1
11. Parkinson's Disease	0	0	0	0	0	0	1	1
12. Eye Disorders	0	0	0	0	0	0	2	2
13. Erectile Dysfunction	0	0	0	0	0	0	1	1
14. Intractable Pain	0	0	0	0	0	0	1	1
CANCER *(BY THERAPEUTIC APPROACH)*	53	3	70	2	7	195	28	358
1. Antisense	4	0	0	0	0	2	0	6
2. Chemoprotection	4	0	4	0	0	4	0	12
3. Immunotherapy/In Vitro Transduction	22	2	19	0	4	57	3	107
4. Immunotherapy/In Vivo Transduction	7	0	28	1	2	80	6	124
5. Pro-drug/HSV-TK and Ganciclovir	12	1	10	0	1	12	6	42
6. Tumor Suppressor Gene	3	0	6	0	0	24	3	36
7. Single Chain Antibody	0	0	2	0	0	0	0	2
8. Oncogene Down-Regulation	1	0	1	1	0	6	0	9
9. Vector-Directed Cell Lysis	0	0	0	0	0	10	6	16
10. Dominant Negative Mutation	0	0	0	0	0	0	2	2
11. Gene Up-Regulation	0	0	0	0	0	0	1	1
12. Radiotherapy	0	0	0	0	0	0	1	1
TOTAL GENE TRANSFER PROTOCOLS *(THERAPY, MARKING and NON-THERAPEUTIC)*	107	7	97	5	12	266	64	*558

Note:** **The total number of protocols on the above list does not equal the total number that has been or will be reviewed by the RAC. Protocol 9903-295 has been withdrawn; Protocol 9907-331 was replaced by protocol 0004-393; Protocols 9910-347 and 9910-348 have been withdrawn; Protocol 9910-349 was replaced by protocol 0010-427; Protocol 0001-374 was replaced by protocol 0007-407; Protocol 0001-375 was replaced by protocol 0010-425; Protocol 0001-377 has been withdrawn; Protocols 0001-383 and 0001-384 have been withdrawn; Protocol 0107-492 was replaced by protocol 0110-499; Protocol 0207-547 has been withdrawn.

Review Level 1 = Full RAC review + NIH Director approval + FDA Investigational New Drug (IND) approval. This review process is no longer in effect.

Review Level 2 = Accelerated RAC Review + NIH Office of Recombinant DNA Activities (ORDA) Approval + FDA IND Approval. This review process is no longer in effect.

Review Level 3 = Sole FDA Review Recommended by NIH/ORDA. Simultaneous submission to NIH(ORDA) required for the purpose of data monitoring and adverse event reporting. This review process is no longer in effect.

Review Level 4 = Sole FDA Review [submission to NIH(OBA) not required]. This is only for non-NIH funded (either direct or collaborative) institutions who elect to submit to NIH(OBA) under voluntary compliance.

Review Level 5 = Received by NIH(OBA). Review level pending.

Review Level 6 = Not Selected for RAC Public Review. Submission to NIH(OBA) required for the purpose of data monitoring and adverse event reporting. This review process is currently in effect.

Review Level 7 = Full RAC discussion + FDA approval. This review process is currently in effect.

Exhibit 2

Selections from

Gene Therapy of Cancer: Methods and Protocols

METHODS IN MOLECULAR MEDICINE™

Gene Therapy of Cancer

Methods and Protocols

Edited by

Wolfgang Walther

Ulrike Stein

Humana Press

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20. **Sexually Transmitted Diseases: *Methods and Protocols,*** edited by *Rosanna Peeling and P. Frederick Sparling*, 1999
19. **Hepatitis C Protocols,** edited by *Johnson Yiu-Nam Lau*, 1998
18. **Tissue Engineering,** edited by *Jeffrey R. Morgan and Martin L. Yarmush*, 1999
17. **HIV Protocols,** edited by *Nelson Michael and Jerome H. Kim*, 1999
16. **Clinical Applications of PCR,** edited by *Y. M. Dennis Lo*, 1998

METHODS IN MOLECULAR MEDICINE™

Gene Therapy of Cancer

Methods and Protocols

Edited by

Wolfgang Walther

Max-Delbrück-Center for Molecular Medicine, Berlin, Germany

and

Ulrike Stein

Max-Delbrück-Center for Molecular Medicine, Berlin, Germany

Humana Press **Totowa, New Jersey**

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31

Gene Therapy for Treatment of Brain Tumor (*HSV-tK* In Vivo Gene Transfer)

A Case Study

Friedrich Weber, Frank Floeth, and Hans Bojar

1. Introduction

Despite a high effort in the research of malignant brain tumors, the clinical results in treatment of malignant brain tumors are still very poor. Brain tumors are a major cause of morbidity and mortality in the population. New primary brain tumors develop in 2–4 of 100,000 adults each year *(1)*. Recent evidence indicates that the prevalence of primary brain tumors is increasing, especially in the elderly *(2)*. The astroglial brain tumors, including the highly malignant glioblastoma multiforme (GBM), are the most common primary brain tumors. For these tumors, the first line of treatment is surgery and almost always radiotherapy as an adjuvant. A variety of patient-management strategies are currently used for GBM, from supportive care to aggressive multimodality approaches. The principal reason for this wide spectrum of approaches is that, despite aggressive therapy, which includes surgical removal of the tumor, postoperative high-dose radiation (60 gy), chemotherapy, and other adjuvant treatments, the prognosis of patients with GBM is very poor *(3–6)*. In a series of NCOG protocols on glioblastoma multiforme patients with Karnofsky performance scores of 60 or higher, who were treated with postsurgical radiation therapy and adjuvant chemotherapy with nitrosourea-based drug combinations, the median survival and time of tumor progression were consistently above 50 and 34 wk, respectively *(7–9)*. The nitrosoureas (BCNU and CCNU), alone and in combination, are the most active cytotoxic drugs for recurrent and progressive tumors, although most of these responses are transient and in patients

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with well-differentiated gliomas. When glioblastoma multiforme recurs, which happens in nearly 100% of all cases, however, the median survival from the start of treatment is about 6 mo, with only 22% of patients surviving longer than 1 yr *(11)*. Therefore, there is a great interest in local treatment modalities. A wafer impregnated with carmustine, for use as an implant after surgical removal of recurrent GBM showed a prolongation in the median survival time of only 2 mo, from 20 to 28 wk in a study with a total of 222 patients. In another study, a median survival of 9 mo was found in a selected group of patients with recurrent GBM who underwent a second operation, but a reasonable quality of life in those patients was limited to 10 wk *(12)*.

Advances in molecular biology and immunology have induced the development of modern immuno- and genetherapeutical strategies. Within different gene therapy strategies is the suicide gene therapy using the herpes simplex thymidine kinase gene. The enzyme thymidine kinase (*tk*) from herpes simplex virus (HSV) are normally not present in human cells,

The *HSV-tK* gene not normally present in human cells, sensitizes transduced cells to ganciclovir (GCV) by adding phosphate to the drug molecule, which is then transformed into GCV triphosphate, which is mistaken by DNA polymerase for deoxyguanosine triphosphate, thus causing chain termination leading to cell destruction. The *HSV-tK* enzyme phosphorylates GCV to a monophosphate form and further phosphorylation by cellular kinases leads to GCV triphosphate compounds that are potent inhibitors of DNA synthesis *(13–15)*. Retroviral vectors encoding the *HSV-tK* suicide gene can be delivered to tumors either by direct injection of viral particles *(16)* or by implantation into the target tissue of cells that continuously produce the virus *(17)*. In this project, living mouse-derived cells that produce large amounts of retroviral vectors carrying the *HSV-tK* gene are injected into brain tumors. New vectors are continuously produced in the tumor for as long as the producer cells survive, therefore, more transduction of tumor cells is expected than with the injection of retroviral vectors alone. For retroviral-mediated in vivo gene transfer, the central nervous system has several advantages of safety and efficacy. Retroviral vectors integrate and, therefore, express vector genes only in proliferating cells. In the brain, the cancer is the most mitotically active tissue and includes the malignant cells and tumor-associated blood vessels, while macrophage-derived cells, blood cells, and endothelial cells have minimal mitotic activity and healthy brain tissue has none. In addition, the brain is a partially immunologically privileged site, which should allow xenogeneic vector-producer cells to survive longer than in other sites and to transduce a very large population of the dividing tumor cells. This immunological "privilege" is further increased because human gliomas are known to depress local immunity

(18). The period of survival of these cells remains however limited—recogniz as xenogeneic, they are eliminated by the immune system, alternatively th would be destroyed by GCV treatment.

2. Materials

2.1. The Retroviral Vector and the Vector-Producing Cell Line

GLI 328 is a retroviral vector-producer cell line containing the *herpes si plex* virus type 1 thymidine kinase gene (*HSV-tK*) and the bacterial neomy resistance gene (*neo'* from Stratagene, La Jolla, CA) in GTI's patented vector backbone. The *HSV-tK* gene is transcribed from the viral Long Terr nal Repeat (LTR), the *neo'* gene, encoding for the enzyme neomycin phospl transferase is transcribed from an internal SV40 (simian virus 40) ea promoter (LTR-*HSV-tK*-SV40–*neo'*-LTR). The *HSV-tK* gene confers sensit ity to the nucleotide analog GCV whereas the *neo'* gene product serves a marker gene and confers resistance to the neomycin analog G418. In th retroviral vector-producer cells, the structural genes of the retrovirus w introduced using the plasmid pPAM3. pPAM3 is a derivative of the Molor murine leukemia virus (MoMLV) and contains the *gag* gene from MoM and a hybrid pol gene from MoMLV and 4070A. The envelope gene in pPA is a hybrid: 82% from the murine amphotrophic 4070A retrovirus, 18% fr an ecotrophic laboratory virus, AM-MLV. To provide the structural prote without generating wild-type retrovirus, further changes were made in structure of pPAM3, so that two recombination events are required to regen ate a wild-type virus. In addition to deleting the packaging signal, the 3′ L from MoMLV was replaced with the SV40 polyadenylation signal and part the 5′ LTR was removed. There is also a mutation in the start codon for gag gene. A producer cell line is made from vector plasmid and packag cells; GLI 328 is a eukaryotic producer cell line and contains the vector pl mid pG1Tk1SvNa stably integrated into PA317 packaging cells. The plasn DNA was extracted from a culture of transformed *Escherichia coli* DH5 The vector plasmid DNA was transfected into an ecotropic packaging c Supernatant from the PE501 transfected cells was then used to transduce 3T3 fibroblast-derived amphotropic packaging cell line PA317. Clones the transduced producer cells were then grown in G418 medium to sel clones that contain the *neo'* gene. The clones were then tested for resista to G418.

It has been discovered that a low percentage of the GLI 328 VPCs contai spliced form of the G1Tk1SvNa provirus. Semiquantitative (polymerase ch reaction) PCR assays performed using primers that specifically amplify

spliced form have established that the percentage of producer cells exhibiting the spliced form is about 1.9%. This level of splice is well below the detection limit of a Southern blot analysis. DNA sequencing shows the spliced form to be a 227 bp sequence bordered by consensus splice donor and acceptor sequences that is deleted from the *HSV-tK* gene. Any truncated protein derived from this spliced *HSV-tK* gene could not phosphorylate GCV.

3. Methods

3.1. Ethics and Good Clinical Practice

Clinical studies have to be performed under standard operating procedures that correspond to GCP conditions. Within Europe, the Rules Governing Medicinal Products in the European Community (directive 91/507/EEC.) and additionally, the U.S. Code of Federal Regulations dealing with clinical studies have to be considered.

3.2. Study Synopsis

Patients suffering from a recurrence of a GBM or showing clinical and radiological evidence of a recurrence of a previously operated malignant glioma, were chosen as a target population (*see* **Notes**).

Primary and secondary study objectives were defined. First, the safety of intracerebral administration of GLI328 followed by GCV treatment should be investigated. Second, evidence of any antitumor efficacy should be assessed by survival as well as time to progression.

3.3. Overall Study Design

This was an open, single group, multicenter, prospective study investigating in a pilot manner the value of *HSV-tK/GCV* gene therapy as an adjuvant to the surgical resection of recurrent glioblastoma in adult patients. The target population was patients with recurrence of a previously resected GBM or a presumption of GBM according to the clinical and radiological characteristics after prior resection of a malignant glioma. In addition, patients were required to meet the selection criteria (*see* **Notes**).

3.4. Shipment of the PA317/G1Tk1SvNa.7 Producer Cells to the Clinical Sites and Handling of the Frozen Material

Dry ice shipments are sent with indicators to monitor the temperature of the container during shipment. If the indicators show that the correct temperature was not maintained during shipment, the product must be destroyed. Upon receipt in the clinical site, the cell bags/cassettes have to be quickly transferred from the shipper to a liquid nitrogen vapor freezer.

3.5. Preparation of PA317/G1Tk1SvNa.7 Producer Cells for Administration to Patients

The product from the freezer bag is processed in a 3-bag wash syste (Baxter Healthcare Corporation, Muskegon, MI, Fenwal Division, FTX-105 Working in a certified laminar flow biological safety cabinet (LFBSC), o spike of the 3-bag wash set is inserted into the spike port of a Ringer's Lacta (RL) bag. After opening the appropriate clamps, 150 mL of RL by weight transferred into one of the bags of the 3-bag wash system. All clamps are clos and the tubing of the spike port is heat-sealed using a hand-held tube seal (SEBRA® Model 2380). The tubing is then cut off, leaving the spike in the RL ba

If it is verified by the surgeon that the patient is ready for surgery, preselected product lot bag/cassette is retrieved from the liquid nitrogen sto age tank. If it has to be transported to the laboratory it has to be placed und dry ice in an insulated box. The bag is removed from the cassette and rapid thawed by immersing in a 37 ± 1°C water bath (calibrated, filled with ster water, without additives) to above the frozen content level. Thawing tak approx 2 min. During this step semifrozen material must not be massaged avoid cell damage. The bag must be kept immersed until the cells are co pletely thawed. Once the cells are thawed, they must be administered with 4 h. As soon as the bag is thawed it is removed from the water bath and has be sprayed with 70–85% ethanol prior to transfer to the LFBSC. After gent mixing of the thawed cell bag, the product is processed in a 3-bag wash syste Using a spike port of the 3-bag wash set, the entire cell suspension of the pro uct lot bag is transferred into one of the empty bags, making sure that no ce remain in the tubing. After closure of all clamps on the wash set, the tubing heat-sealed just below the Y and the empty product lot bag is discarded. T clamps of the cell bag and the RL bag are then opened and 40 mL of RL weight are transferred to the cell bag over 45 s while mixing. All clamps a closed. The cells are pelleted by placing the 3-bag wash set into a precool centrifuge (Beckman J-6B, rotor JS 4.2, Fullerton, CA) and spinning at 1100 rp for 5 min at 4 ± 2°C. The wash supernatant is then expressed from the cell b into the waste bag of the 3-bag system by use of a plasma extractor (Baxt Healthcare Corporation, Fenwal Division), taking care that no cells go into t waste bag. After closure of the clamps of the cell bag and waste bag, t pelleted cells are resuspended by gently massaging the cell bag. The clamps the cell bag and RL bag are then opened and 40–50 mL of RL are transferred the cell bag by weight. After closure of all clamps, the cells are mixed by ma saging and the described steps are repeated for a second and third wash. Aft the final waste expression using the plasma extractor, cells are left in appr

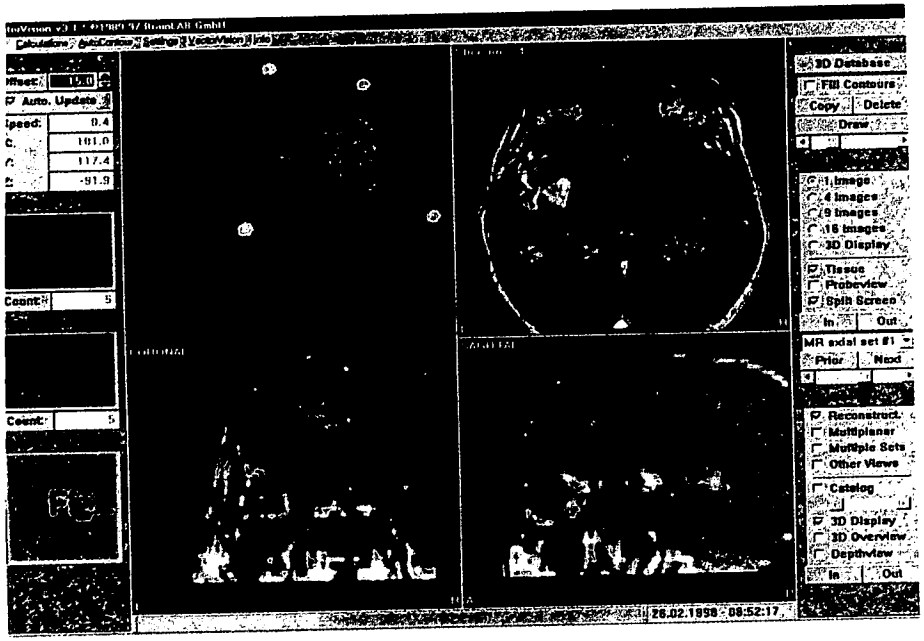


Fig. 1. Resection area and installation area was carefully planned using three-dimensional reconstructions of CT/MRI scans.This procedure provides the surgeon with more safety during the surgical procedure. The VPC can be administered with higher accuracy.

10 mL. After closure of the clamp on the cell bag, the cells are resuspended by massaging. After appropriate heat-sealing, the cell bag is cut off from the 3-bag wash set. Working in the LFBSC, a sampling site coupler is inserted into the cell bag. The total volume of washed cell suspension is determined by weighing. An aliquot of the cell suspension is removed for cell counts. The cell bag has to be kept on ice while counting cells. For cell count, 0.1 mL of cell suspension is added to 49.9 mL of diluted Trypan blue (0.4%, Sigma, St. Louis, MO). Using brightfield optics, viable and nonviable cells are counted in a hemacytometer (Neubauer improved). The cells should appear spherical with neither swelling nor shrinkage.

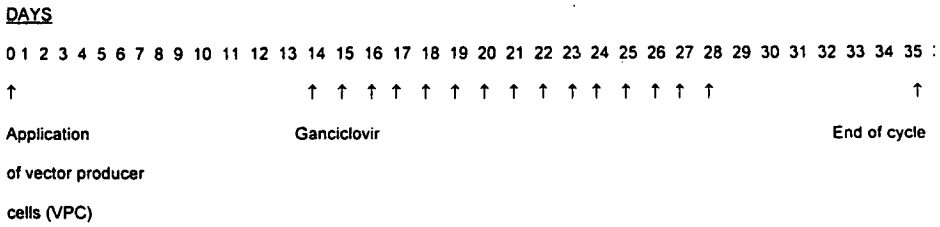
If the requirements for yield ($\geq 0.9 \times 10^9$ cells in a total volume of about 9 mL) and viability (≥75%) are met, the cell bag is placed into an isolated ice container for transport to the operating room.

3.6. Experimental Treatment

The therapy was initiated by a gross total resection (**Fig. 1**), whereby the opening of the ventricles should be avoided. After resection, the cavity wall

Fig. 2. Procedure of application of VPC after tumor debulking into the tissue adja cent to the recection border.

was infiltrated by 50 single injections (**Fig. 2**) in a depth of 1.5 cm (*see* **Notes**) The injections were homogenously distributed over the whole surface. The tumor tissue was histopathological examined during the surgical procedure Only when the assumed diagnosis was histologically verified, the administration of the vector producer cells was performed. Preoperatively, the tumor was neuroradiologally evaluated by MRI scan. In order to get a good discrimination between residual tumor and unspecific contrast enhancing owing to breakdown of the blood-brain barrier, the first postoperative control was performed within 24 h. GCV treatment was started 14 d after surgery over a period of 14 d (5 mg/kg twice a day):



'umoral tissue taken at surgery underwent central histopathological examion. Ganciclovir, was given twice daily as an iv perfusion between days 27. MRI scans were carried out immediately before surgery within 48 h r resection, on day 35, every second month until month 12, and thereafter ry 3 mo. Clinical and routine blood examinations were repeated at weekly rvals until day 35, at month 2, every 2 mo until month 12, and thereafter ry 3 mo. Blood samples for biosafety monitoring were taken at baseline, 14 (for the first 10 patients only), day 35, every 2 mo until month 12, and n annually for life. Brain tissue samples were to be obtained at subsequent ction or at autopsy and CSF and other tissue samples whenever possible. biosafety testing was aimed at detecting the presence of transduced nor- l cells, the presence of recombination events leading to the formation of lication competent retrovirus, as well as the presence of antibodies to either vector-producer cell or the retroviral vector core protein. The samples were zen immediately after being obtained, shipped and stored in liquid nitrogen. entral neuroradiologist reviewed the MR scans of all patients in a sequenmanner.

. Posttreatment

Patients were to be seen as out-patients at months 2, 4, 6, 8, 10, and 12 after cell injection, then every 3 mo for the second year, and then at least annu- until they terminated the study or died. Each of these evaluations was to lude the following evaluations, unless stated otherwise.

Complete physical examination.
. Karnofsky assessment.
. MRI or CT scan of the brain.
Laboratory assays: hematology, chemistry, urinalysis.
. Collection of samples for biosafety monitoring: whole blood (uncoagulated for the isolation of PBLs at the central laboratory), frozen serum, and autopsy samples where possible.
Annual visits after 24 mo of follow-up to include collection of biosafety samples for study specific evaluations.
. If, at any time, the patient underwent reresection of the tumor, tissue was to be obtained for biosafety analysis.

. Efficacy Variables

Survival time was estimated by measuring the time interval from surgery l administration of GLI 328 to death. The response of the tumor was to be ed on the quantification of the tumor-enhancement volume observed on her MRI or CT scans. Response was to be estimated according to the follow- criteria: complete response (disappearance of all detectable malignant

disease); partial response (>50% decrease in volume); minor respons (25–49% decrease in volume); stable disease (<25% decrease 8 <25% increas in volume); locally progressive disease (>50% increase in volume or develop ment of new lesion locally); and nonlocally progressive disease (developmen of a new tumor or >50% increase in volume of a tumor which is noncontiguou with the treated tumor).

Quality of survival was estimated by monitoring the Karnofsky performanc score (KPS). This was defined as the time since surgery and GLI 328 injectio until the sustained fall in the KPS to below 40. The same analysis was done fo a KPS threshold of 60.

3.9. Biosafety Monitoring

3.9.1. Detection of Vector in Peripheral Blood Leucocytes (PBL) by PCR

1. PBL DNA was tested for vector-specific proviral sequences using a PCR assa with primers specific to the *NeoR* gene or *HSV-tK* gene.
   a. The assay sensitivity was validated to detect one copy per 500,000 cells. At set detection limit of 10 copies, the assay was capable of detecting 10 or mor copies of proviral vector DNA with a confidence of 99.99%.
   b. To distinguish between transduced lymphocytes and VPCs, all positive result were tested for the presence of *env* helper sequences, which are only presen in VPCs.
2. Detection of replication-competent retrovirus (RCR) DNA sequences by PCR PBL DNA was tested for the presence of RCR-specific proviral sequences usin a PCR assay with primers selected to detect recombinant RCR, but not vecto proviral DNA or producer-cell DNA.
   a. The assay sensitivity was validated to dectect one copy per 500,000 cells. A a set detection limit of 10 copies, the assay was capable of detecting 10 o more copies of proviral vector DNA with a confidence of 99.99%.
3. Cocultivation for detection of RCR. Peripheral blood mononuclear cells (PBMC were cocultured with *Mus dunni*, a murine cell line permissive for a range o viruses. If PBMCs produced RCR, the *Mus dunni* cells would become infecte from RCR virions shed from the patients' PBMCs leading to cell death that coul be observed in culture.
   a. The assay sensitivity was validated to detect 50 RCR positive cells pe 10,000,000.

4. Notes

1. Before starting therapy, the patients were carefully evaluted regarding tumo localization and extension. If the lesion involved both hemispheres, the corpu callosum, the brainstem, or was in close approximity of the ventricular system the patient was excluded from the study.

If the ventricular system was opened during surgery, no vector-producing cells were administered because of the occurrence of some neurotoxic events when VPC had been administered intrathecally. With respect to feasibility, multiple injections of small volumes of VPC suspension into the resection cavity wall were technically complicated by the need to ensure that the injection tracks were evenly distributed and as perpendicular as possible to the cavity wall. Inevitably, with the irregular nature of the cavity some overlapping of the tracks occurred whereas other zones were nearly inaccessible. Although the aim was to inject the maximum volume, injection varied depending on the size of the cavity.

The greatest problem, however, was that of reflux, which was extremely variable. The declared injected volume is likely to be an overestimate of the actual amount retained in the brain tissue because of the reflux of suspension up and out of the injection track in many cases.

Additionally, the penetration of VPCs beyond the injection site is limited to several mm and presents a major problem regarding in vivo transduction efficacy. As primary safety concerns treatment-related CNS events, brain lesions or hemorrhage because of mechanical stresses of multiple injections of VPCs have to be considered. Inflammatory reactions resulting from the application of xenogenic cells have not occured.

erences

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Intratumoral Gene Transfer of the Cytosine Deaminase Gene for the Treatment of Breast Cancer

Hardev S. Pandha and Nicholas R. Lemoine

1. Introduction

One of the major limitations of conventional cancer chemotherapy is its lack of selectivity; there is cytotoxicity to both tumor cells and normal cells. Genetic prodrug activation therapy (GPAT) uses transcriptional differences between normal and neoplastic cells to drive the selective expression of a metabolic suicide gene able to convert a nontoxic prodrug into its toxic metabolite. Genetically modified cells that express the nonmammalian enzyme cytosine deaminase (CD) gene are able to convert the nontoxic prodrug 5-fluorocytosine (5-FC) to the toxic metabolite 5-fluorouracil (5-FU), which inhibits RNA and DNA synthesis during S-phase of the cell cycle *(1,2)*. We have devised a transcriptionally targeted GPAT strategy in which expression of CD is restricted to ERBB2-expressing tumor cells. Exposure of CD-expressing cells to 5-FC should result in tumor-selective cell kill thereby sparing normal breast cells.

ERBB2 protein plays a crucial role in the pathogenesis of many human cancers such as breast, pancreas, lung, and ovarian carcinomas. Overexpression of ERBB2 in 25–30% of breast carcinomas is associated with reduced relapse-free and overall patient survival *(3)*. High ERBB2 receptor levels has been shown to correlate with poor prognosis in node-positive patients *(4,5)*, in a subset of node-negative patients *(6,7)* and in entire cohorts irrespective of nodal involvement *(8)*. ERBB2 status has also been predictive of resistance to endocrine and cytotoxic therapies *(9–11)*. Overexpression of ERBB2 is owing both to increased gene transcription and gene amplification. The activity of the ERBB2 promoter is enhanced in overexpressing cells through binding of

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members of the AP-2 family of transcription factors to a response element in the proximal part of the promoter. We have previously shown that a 500 base-pair fragment of the proximal promoter (containing the AP-2 binding site) driving the CD gene transduced into a panel of breast and pancreatic tumor cell lines, resulted in levels of CD expression and cell death (upon exposure to 5-FC) directly proportional to the ERBB2 status of the cells *(12)*. The recent availability of a monoclonal antibody (16D8F2) to bacterial cytosine deaminase has allowed direct examination of *Escherichia coli* CD protein expression in clinical biopsy tissue by immunohistochemistry *(13)*. In previous in vitro and murine studies, it has only been possible to monitor CD expression indirectly by cell killing or enzymatic assays *(14,15)*.

1.1. Clinical Protocol

The aim of the clinical study is:

1. To establish a safe and effective dose of a recombinant ERBB2-CD chimaeric gene to sc breast cancer metastases.
2. To confirm the expression of CD in injected ERBB2-positive sc breast cancer metastases.
3. To determine the ability of metastases expressing CD to activate 5-fluorocytosine to 5-fluorouracil.
4. To examine the effects of the local release of 5-fluorouracil on tumor growth in subcutaneous nodules.

1.1.1. Inclusion Criteria

Patients require:

1. At least three well demarcated, nonulcerating skin metastases less than 2 cm diameter.
2. Histologically proven cutaneous relapse of breast cancer.
3. Good performance status (WHO 0, 1, or 2).
4. Normal renal and haematological parameters.
5. Life expectancy of at least 3 mo.
6. Failure on conventional treatment (radiotherapy, endocrine therapy and at least one systemic form of chemotherapy) with an interval of at least 4 wk since previous chemotherapy.
7. Positive ERBB2 status established by immunohistochemistry using two antibodies to the human ERBB2 receptor, which should give concordant results. Only membrane-associated (and not cytoplasmic) staining is considered significant. A positive result to qualify for trial entry is taken as membrane immunoreactivity in at least 30% of tumor cells *(16)*. Previous studies have shown that membrane immunoreactivity correlates with at least threefold overexpression compared to normal breast. The degree of overexpression of ERBB2 by immunohistochemistry was designated according to the proportion of tumor cells expressing the oncoprotein: moderate(+) staining indicated up to 30% of all tumor cells positive, intermediate(++) 30%–70%, high degree of positive staining (+++) over 70%.

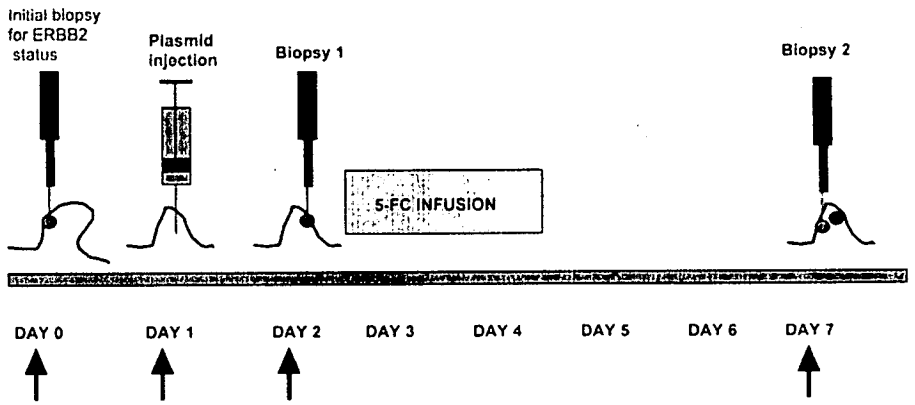

Fig. 1. Schematic representation of the clinical schedule. Three discrete well-demarcated nonulcerating skin lesions are selected, measured, marked, and photographed. After an initial biopsy for ERBB2 status lesions, two of the three lesions are injected with pERCY or polyNeo plasmid in 0.2 mL of sterile water. This is directed into the centre of the tumor nodules using a 22-gage needle. The third lesion selected is the uninjected control. A biopsy is taken from the injected nodules after 24 h and the 2-d 5-FC infusion commenced after 48 h (for the first eight patients only). Further biopsies, measurements, and photographs are taken 7 d after initial intralesional injections.

1.1.2. Exclusion Criteria

1. Systemic progression of disease.
2. Active autoimmune disease.
3. Concomitant infection with hepatitis virus or HIV.
4. History of psychiatric illness that could influence compliance.
5. Documented presence of cerebral metastases.
6. If chemotherapy given within previous 4 wk.
7. Anaemia or leucopenia as a result of recent chemotherapy.

1.1.3. Clinical Schedule

The clinical schedule is shown in **Fig. 1**.

1. Three similar-sized discrete lesions are marked, measured, and photographed.
2. One lesion is injected with pERCY plasmid containing the proximal ERBB2/CD chimera, the second with the control plasmid polyNeo, which has the same plasmid backbone as pERCY with the ERBB2 promoter/CD chimera removed. The

third lesion is not injected and served as a further control. All injections were in 0.2 mL of sterile water and directed into the center of the tumor nodules using a 22-gauge needle.
3. A biopsy is taken from the injected nodules at 24 h.
4. Infusion of 200 mg/kg/24 hr 5-FC (Alcobon, Roche) prodrug is commenced after 48 h, and given for a total of 48 h duration.
5. Further biopsies, measurements, and photographs are taken 7 d after initial injection.

Responses to GPAT are evaluated clinically (e.g., changes in shape of nodules), by two perpendicular measurements of the tumor nodule diameters and by clinical photography. Complete tumor response is defined as the complete disappearance of the injected cutaneous tumor nodule; partial response is defined as 50% or greater reduction of the sum of the products of perpendicular diameters. Biopsies are taken posttreatment on day 2 and day 7 using a 3-mm punch biopsy. The tissue is orientated and divided longitudinally using a sterile scalpel. One half was snap frozen in liquid nitrogen, the other fixed in formalin and paraffin-embedded the same day.

2. Mat rials

2.1. The Plasmids Used

For this clinical study, a 544 bp DNA fragment of the proximal 5′ flanking region of ERBB2 (containing the promoter response element) was isolated as described by Hollywood and Hurst *(17)* and cloned into pBluescript II SK+ (Strategen Ltd., Cambridge, UK). A 1522 bp DNA fragment encoding *E. coli* cytosine deaminase was cloned downstream of the 544 bp DNA fragment of ERBB2 to produce and intermediate plasmid pERBB2. The plasmids used for patient injection were based on the commercially available vector pcDNA3. The 2.1-kb chimaeric minigene comprising the ERBB2 promoter response element and the CD gene was subcloned into pcDNA3 into the *Bam*HI restriction site after the CMV promoter/enhancer had been removed, and was designated pERCY. The control plasmid polyNeo was created by *Bgl*I and *Bam*HI digestion of pcDNA3 to remove the CMV promoter/enhancer and religation of the free ends which destroyed the *Bam*H I restriction site. The plasmid constructs used in clinical trial are shown in **Fig. 2**.

3. Methods

3.1. Immunocytochemistry to Establish ERBB2 Status

This may be performed on fresh biopsy tissue or paraffin-embedded archival tissue. Two antibodies to the human ERBB2 receptor should be used such as those supplied by Dako (High Wycombe, U.K.) or Signet (Cambridge,

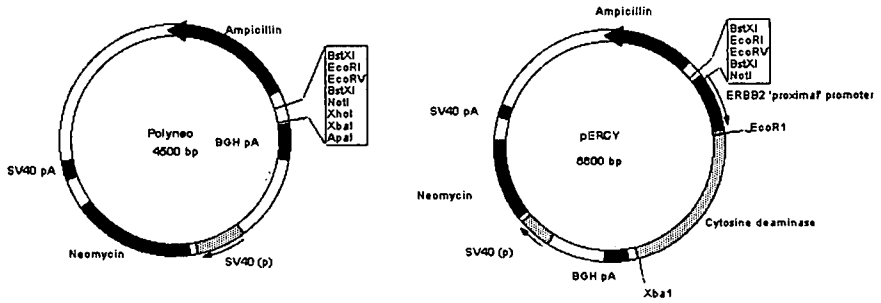

Fig. 2. Plasmid maps of the constructs used in the clinical trial.

U.K.), and should give concordant results. A positive result to qualify for trial entry is taken as membrane immunoreactivity in at least 30% of tumor cells.

1. Mount biopsy tissue onto polysine-coated or Vectabond-coated (not polylysine) slides.
2. Block endogenous peroxidases by incubating slides in 0.3% H_2O_2 for 15 min.
3. Reduce nonspecific binding of ERBB2 antibody by blocking in normal goat serum at 1/20 dilution for 30 min.
4. Incubate in primary antibodies diluted according to the manufacturer's recommendation at 4°C overnight; Dako 1:3000 and Signet 1:100.
5. Incubate for 30 min at room temperature with the appropriate biotinylated secondary antibody (for Dako swine antirabbit, for Signet goat antimouse).
6. Label with peroxidase-streptavidin at 1:500 dilution for 30 min at room temperature.
7. Incubate slides in diaminobenzidine (DAB) chromogen for 10 min. Positive immunoreactivity is visible as brown staining.

3.2. Immunocytochemistry to Detect Cytosine Deaminase in Cells and Tissues

This is performed initially on cell lines (to provide positive and negative controls) before evaluating cryostat cut sections of snap-frozen tissue from clinical biopsies.

1. Fixed and permeabilize both cultured cells grown on sterile glass slides and tissue sections.
2. Incubate slides/sections in 3% paraformaldehyde/PBS for 5 min and then in 0.05*M* NH4Cl/PBS both at room temperature.
3. Incubation in cold absolute methanol at –20°C for 10 min, followed by permeabilization in 0.1% Triton-X-100/PBS at room temperature for 5 min.
4. Incubate in primary monoclonal antibody 16D8F2[18] diluted 10 µg/mL for 30 min at room temperature.

5. Incubate in secondary antibody (biotinylated goat antimouse).
6. Label with peroxidase-streptavidin at 1/500 dilution for 30 min at room temperature.
7. Incubate slides in DAB chromogen for 10 min. Positive immunoreactivity is visible as brown staining.

It is recommended that the antibody is initially tested on cells transfected with the CD gene as well as the nontransfected line (negative for CD). The biopsy samples the degree of CD expression by immunohistochemistry is designated according to the proportion of tumor cells expressing the CD protein: (+++) indicated over 70% of tumour cells positive, (++) 50–70% positive, and (+) less than 50% positive.

3.3. In Situ *Hybridisation for Cytosine Deaminase mRNA Detection*

Cytosine deaminase mRNA expression in paraffin-embedded clinical trial biopsy tissue may be determined by an *in situ* hybridization technique (based on Senior et al. 1990) ***(18)***.

3.3.1. Preparation of Slides

1. Wash microscope slides held in a metal slide rack and coverslips overnight in 10% Decon-90, then in hot running tap water for 60 min, and finally rinse in milli-Q water prior to baking slides covered in aluminium foil at 180°C for 4 h.
2. Immerse slides for 10 s in freshly prepared 3-aminopropylethoxysilane (TESPA, Sigma) 2% (v/v) in acetone, then rinse twice in acetone and twice in DEPC-treated water prior to drying in an oven at 40°C. Discard remaining TESPA as only freshly prepared solution should be used.
3. Cut 4 µm sections from paraffin-embedded biopsies using a microtome and float on DEPC-treated milli-Q water. Use disposable microtome blades or ensure rigorous cleaning of the blade with alcohol prior to use. Collect sections onto TESPA-coated slides and oven-dry overnight at 40°C. Coverslips are washed in 70% alcohol in a metal rack and oven-baked at 180°C for 4 h.
4. De-wax sections in fresh xylene and 0.1% DEPC for 8 min, and then rehydrate through 100%, 80%, 60%, and 30% ethanol containing 0.1% DEPC.
5. Permeabilize tissues with proteinase K (final concentration 20 µg/mL) in PBS 37°C for 10 min, and rinse in 2X PBS containing 0.2% (w/v) glycine for 5 min.
6. After two further rinses in PBS, fix sections in 4% paraformaldehyde in PBS for 20 min (*see* **Note 1**).
7. Rinse in PBS twice.
8. Acetylate sections with 500 mL 0.1*M* triethanolamine and 1.25 mL of acetic anhydride. Mix well for 10 min.
9. Wash slides in PBS 3 more times for 5 min, and dehydrate through graded alcohol from 30% to 100% containing 0.1% DEPC.
10. Air-dry sections prior to hybridization.

3.3.2. Preparation of ^{35}S-labeled Riboprobes

1. Add 1 µg of each restriction digest template to the in vitro transcription mix: (1X transcription buffer (Promega, Madison, WI), 1.5 U/mL RNAsin (Promega), DTT (5.6 m*M* plus 5.6 m*M* from ^{35}S-UTP), ATP, GTP, CTP mix (each 6.25 µ*M*), 10 U/µg template of RNA polymerase plus 3.5 µL (800 Ci/mmol) ^{35}S-UTP (Amersham, Arlington Heights, IL).
2. Incubate this mixture plus templates at 37°C for 60 min.
3. Destroy the template by adding 1 µL of DNase I (RNase free) to the reaction tube and incubating for 15 min.
4. Dilute the reaction mix in 25 µL of 10 m*M* DTT and 1.5 µL of ribosomal RNA (10 µg/mL used as a carrier).
5. Take 1 µL into 50 µL of water and 3 mL scintillant to assess total ^{35}S present.
6. Equlibrate a Chromospin-30 column (Clontech, Palo Alto, CA).
7. Add the bulk of the reaction mix to the column, spin at 700*g* for 3 min at 15°C and collect eluate.
7. Add 4 µL of 100 m*M* DTT, mix well then count 1 µL in 50 µL water and 3 mL scintillant: calculate the percentage incorporation of ^{35}S (should be 40–80%)
8. The riboprobe eluate is assessed for quality on a 6% polyacrylamide sequencing gel and, if satisfactory, stored at –20°C until required (*see* **Note 2**).

3.3.3. Hybridization

The hybridization buffer consists of 10% 10X salts mix in Denhart's solution, 50% formamide, 3% rRNA, 20% dextran sulphate, 1% 1*M* DTT, and the remaining 16% of the total volume of the probe is made up with DEPC-treated milli-Q water.

1. Heat the hybridization buffer containing the probe to 80°C for 1 min.
2. Pipet 20 µL of hybridization buffer onto each slide.
3. Place slides in a humidified box containing blotting paper saturated with 1X salts and 50% formamide. Seal box with tape and incubate overnight at 55°C.
4. After hybridization, place slides in 50% formamide at 55°C for 4 h, then wash slides for 5 min 10 times using TNE buffer.
5. Incubate slides in 100 µg/mL RNase A in TNE buffer solution at 37°C for 1 h.
6. Wash slides in 2X SSC and 0.5X SSC each for 30 min at 65°C.
7. Finally, to ensure that the labeled hybrids remain in place, pass the slides through graded ethanols increasing from 30% to absolute ethanol all containing 0.3*M* ammonium acetate.
8. Air-dry slides overnight prior to autoradiography.

3.3.4. Autoradiography and Slide Developing

For the autoradiography process, melt 25 mL of Ilford K5 emulsion in 2.4 mL of 5*M* ammonium acetate, and dilute with 25 mL of milli-Q water warmed to 45°C.

1. Dip slides into the emulsion to cover the tissue, then cool and dry in total darkness by placing slides on a metal plate overlying ice.
2. Once dry, place slides in a plastic rack, sealed in a light-tight bag and expose for 15 d at 4°C.
3. Develop slides in Kodak D-19 developer at 18°C for 4 min and fix in 30% sodium thiosulphate.

3.3.5. Counterstaining

The Giemsa stain discriminates individual cell structures. Giemsa staining of slides in parallel to those used for *in situ* hybridization are prepared by immersing slides in dilute stock Giemsa solution (1 in 100 with distilled water) for 60 s. Excess stain is washed off with tap water and the slides air drying prior to examination.

The CD gene required for preparation of the riboprobes for this *in situ* work was directionally cloned into pGEM-4 vector using the *Eco*RI and *Hind*III sites. Linearized pGEM-4 containing a 428 base pair CD insert was used for in vitro transcription of the riboprobe with:

1. *Eco*RI for production of sense strand (negative control) under control of the T7 promoter.
2. *Hind*III for production of antisense strand under the control of the SP6 promoter.
3. Linearized pBluescript containing β-actin cDNA with *Dra*I, also under the control of the SP6 promoter.

The digestion products were phenol/chloroform extracted and ethanol precipitated. The activity of radiolabelled probes eluted from Chromaspin-30 columns were assessed in a scintillation counter and were between 3.0×10^6 cpm and 3.65×10^6 cpm. All sections should be examined with CD sense, CD antisense, and β-actin antisense probes.

3.4. Quantitative Assay for Cytosine Deaminase Activity In Vitro

To detect cytosine deaminase activity in either cell lines expressing CD or in clinical biopsies, a thin layer chromatography method (TLC) was developed. The method relies on the enzyme's ability to convert cytosine to uracil; a reaction which merely converts the amine group to a ketone group. The two compounds have different mobilities through a liquid phase (in this case a mixture of butanol and water). These compounds can be radioactively labeled and separated by TLC. The method was modified from that described by Andersen and co-workers *(19)* (*see* **Note 3**).

1. A minimum of 1×10^6 cells are washed in Hanks Balanced Salt Solution and resuspended in 200 µL of lysis buffer (100 m*M* Tris-Cl pH 7.8, 1 m*M* EDTA, 1 m*M* dithiothreitol).

2. Freeze/thaw lysates by immersion in liquid nitrogen, and centifuge at 15,800*g* for 10 min.
3. Take 10-µL aliquots of cleared lysates and mix with 10 µL of "cytosine label mix" (consisting of 0.97 mCi, 12.2 Ci/mmol [^{3}H]-cytosine in 100m*M* Tris-Cl, pH 7.8).
4. Incubate lysates in the presence of [^{3}H]-radiolabeled cytosine for 1 h at 37°C, then spot 5–10 µL onto fluorescent TLC sheets (Merk, plates 1.05735).
5. Spot nonradioactive standard samples of cytosine and uracil (0.4 mg/mL) at either ends of the TLC plate. Because these absorb UV light, their positions on the TLC plate can be estimated using a hand-held UV source (λ^2 240 nm).
6. Place the TLC sheets in a chromatography chamber containing butan-1-ol and water (86:14 v/v), seal the chamber with clingfilm and allow to run for 4 h (*see* **Note 4**).
7. To calculate rate of uracil formation, cut out bands corresponding to the radioactive products (i.e., at the level of the nonradioactive uracil control) and place in scintillation tubes containing 5 mL of liquid scintillation analyzer (TriCarb 1500). Measure radioactivity by scintillation counter.
8. The amount of radioactivity recovered from the cytosine and uracil bands should account for all of the label introduced. This is confirmed by assaying activity of the same amount of label not separated by chromatography. The percentage conversion of cytosine to uracil over the time period is calculated as the amount of uracil produced divided by the amount of cytosine substrate introduced into the reaction. Each time-point gives a value in radioactivity, which is converted to the amount of uracil produced at each time point and the results plotted on a graph. The gradient of the resulting line is the rate of deamination, i.e., the enzyme activity, because this may be expressed as product/amount of cells/time period. A typical result of TLC using CD-expressing cells lines HPAF CD500 and control HPAF cells is shown in **Fig. 3**; deamination of radiolabeled cytosine results in cytosine to uracil conversion by the CD-expressing cell line only.

The conversion of cytosine to uracil expressed as a percentage is calculated as:

$$\text{\% conversion to uracil} = \frac{\text{dpm uracil band}}{\text{total dpm in uracil and cytosine bands}} \times 100\%$$

(dpm = decay per minute)

4. Notes

1. The paraformaldehyde should be made up fresh for each experiment. In order to ensure the 4% solution dissolves completely, the paraformaldehyde is added to PBS that has just boiled, then the 4% solution is allowed to cool gently at room temperature.
2. For 100% incorporation, total incorporated counts will be 3.2×10^8, equivalent to 243 ng RNA. Expect 10 million dpm (decay per minute)/mL. One million dpm is approximately 0.7 ng RNA probe. Specific activity of RNA transcript will be $1.3–1.7 \times 10^9$ dpm/µg RNA using the ^{35}S as the only source of UTP.

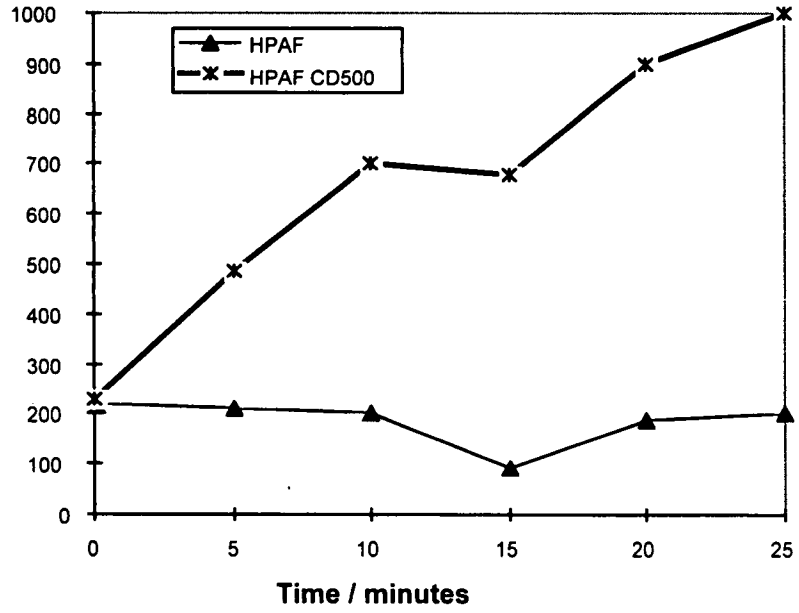

Fig. 3. Example of a quantitative assay for cytosine deaminase activity in vitro by conversion of cytosine to uracil in HPAF CD500 cell line compared to HPAF parental cells.

3. It is recommended that determination of CD activity is performed initially on CD-transduced and control cell lines to determine the sensitivity of the technique.It will be possible to evaluate the minimum number cells required for detection of converted uracil before committing clinical tissue. In our experience this technique requires a minimum of 1 million cells.
4. The TLC should be run in a fume cupboard as butan-1-ol fumes are irritant. To ensure uniform movement of all bands it is important to ensure that the TLC plate is surrounded by a butan-1-ol atmosphere within the chromatography chamber. This is best achieved by sealing the chamber using either a heavy glass lid with Vaseline smeared onto the rim of the chamber, or several layers of clingfilm.

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Adenovirus-Mediated Wild-Type *p53* Gene Transfer into Head and Neck Cancers

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1. Introduction

Mutation of the *p53* tumor-suppressor gene is recognized as one of the most common genetic alterations in human malignancy to date *(1)*. Approximately 60% of human tumors are thought to possess mutation at the *p53* locus. Transient overexpression of the wild-type *p53* gene in various malignancies has been considered a potential molecular intervention strategy *(2–7)*. This strategy is based on the role that wild-type *p53* plays as a tumor-suppressor gene and inducer of cell-cycle arrest and apoptosis *(1,8–11)*.

Previous work in our laboratory has focused upon the potential of wild-type *p53* gene transfer as a strategy for the selective induction of apoptosis in human head and neck squamous cell carcinoma of the upper-aerodigestive tract (SCCHN). The recombinant adenovirus, Ad-p53, has been used as the gene delivery tool in all of our preclinical and clinical studies. This replication-defective vector has been described in detail elsewhere *(4)*. The tropism of adenovirus for tissues of the upper-aerodigestive tract make it an ideal gene-delivery vehicle for our purposes. It is important to point out that the genetic material introduced into mammalian cells via Ad-p53 remains episomal (not integrated into the DNA) and is overexpressed. Gene expression is transient as the episomal DNA is not passed on to daughter cells.

Our interest in new treatment strategies for SCCHN is generated by the humbling survival rates (50%) for these tumors, which have not changed over the last several decades with current standard treatment modalities (radiation, surgery, chemotherapy) *(12)*. Furthermore, after undergoing standard therapy (including radiotherapy), the SCCHN patient with recurrent disease has a

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particularly dismal prognosis and has few meaningful treatment options. The principal cause of death in SCCHN is local-regional recurrence *(13,14)*. Clearly, new treatment strategies need to be developed and investigated. Thus, the study of novel molecular therapies involving genes such as wild-type *p53* seemed appropriate. The fact that local-regionally recurrent SCCHN is readily accessible, even in the most advanced cases, enhanced its candidacy for investigation as a target for wild-type *p53* molecular intervention.

Our preclinical laboratory investigations demonstrated that introduction of the wild-type *p53* gene via Ad-p53 into SCCHN cell lines and established tumor nodules in nude mice suppressed in vitro and in vivo tumor growth, respectively *(4)*. Further studies demonstrated that this suppression of cell growth was via cell death, and that the mechanism of cell death was apoptosis *(3)*. Our group was able to demonstrate that the apoptotic process occurred in malignant cells regardless of their *p53* status, albeit at different rates. Furthermore, normal fibroblasts were not sensitive to these effects, suggesting that the induced apoptotic process was selective for malignant cells *(2)*.

The results of the preliminary data regarding wild-type *p53* molecular therapy in our laboratory led to investigating its utility in a residual SCCHN murine model *(2)*. Such a model was developed secondary to the high incidence of locoregional failure in this disease, presumably secondary to microscopic residual disease following initial standard therapy. Introduction of Ad-p53 locally into sites of SCCHN tumor cell inoculation in nude mice prevented the establishment of tumors. This study (and its precursors) laid the groundwork for the current adenovirus-mediated wild-type *p53* human gene therapy trial at the Department of Head and Neck Surgery, University of Texas M.D. Anderson Cancer Center, for patients with advanced local-regionally recurrent head and neck squamous cell carcinoma of the upper-aerodigestive tract that has failed other standard therapeutic modalities. The first phase of this trial has been completed, and an international phase II trial has been initiated.

As aforementioned, patients with local-regionally advanced, recurrent SCCHN that have failed initial standard therapy have a dismal prognosis. If radiation was included in the treatment regimen for such patients, they are furthermore left with few therapeutic options. Patients with these characteristics formed the study population for our Ad-p53 clinical trial. Thus, we present our materials and methodology for the administration of Ad-p53 molecular therapy in the management of SCCHN within the context of our phase I clinical trial.

Patients in phase I were randomized into two treatment arms. The first arm consisted of inoperable patients. The second arm consisted of patients who were deemed operable but incurable. The patients in the second arm received Ad-p53 preoperatively in six doses over 2 wk and then intraoperatively and postoperatively as an adjuvant approach to the surgical extirpation of their

recurrence. For simplicity, we will discuss the administration of Ad-p53 molecular therapy in the management of SCCHN in the context of the patients in this second treatment arm.

2. Materials

The replication-defective recombinant adenovirus, Ad-p53 was utilized for all wild-type *p53* gene transfers. This vector contains the cytomegalovirus (CMV) promoter, and wild-type *p53* cDNA in a minigene cassette inserted into the E1-deleted region of human adenovirus, type 5. Details regarding the preparation of recombinant adenovirus can be found in the publication Zhang et al. *(15)* Ad-p53 is a BL-2 agent and should be handled with the appropriate level of biological containment. After production, Ad-p53 was stored at –80°C at concentrations of 2–3.5 $\times$ 10^{10} particle forming units (pfu) per mL in phosphate-buffered saline (PBS) supplemented with 10% glycerol in the hospital pharmacy. Ad-p53 was thawed and diluted in PBS at 4°C within 2 hours of use.

All staff wore glasses, gowns, and gloves at the time of administration of Ad-p53. Hepa masks (3M Corp., St. Paul, MN), fit tested and 99% efficient respirators, were also worn at the time of vector delivery to patients (*see* **Note 1**). Technol 2010 masks (Technol Inc., Fort Worth, TX), not fit tested and 95% efficient respirator, were worn while in the room with patients subsequent to vector delivery for the purposes of patient monitoring and blood draws. Ad-p53 administration was carried out with sterile 5–10 mL syringes and 27-gauge needles. The vector was drawn out of the stock vials (containing 2–3.5 $\times$ 10^{10} pfu per mL) using 18-gage needles for the purposes of dilution.

3. Methods

In phase I of the clinical trial, all Ad-p53 administration was performed on an inpatient basis. The first cycle consisted of treatments (direct tumor injections) given three times weekly for 2 wk, excluding weekends (six treatments overall). Seventy-two hours following the last treatment in the first cycle, patients had surgery. At the time of surgery and just prior to closure, an administration of a single dose of Ad-p53 was delivered to the surgical bed and left in contact for 60 min. Seventy-two hours after surgery, a retrograde instillation of Ad-p53 was administered through wound catheters, which had been placed intraoperatively.

3.1. Administration of Ad-p53

The clinical trial was designed in a dose escalation manner in order to determine a maximum tolerated dose per treatment. Whereas patients early in the study received 1 $\times$ 10^{6} pfu total to the tumor (or tumor bed) during each treatment (including each of the six treatments of the first cycle), doses were

increased in log increments until 1×10^9 pfu was reached, and then in one-half log increments until 1×10^{11} pfu was reached.

1. After acquiring the Ad-p53 stock vial(s) from the pharmacy for a given patient treatment, the sample was thawed. The pharmacy stock vials were prepared as 2×10^{10} pfu in 0.1 mL to 1 mL PBS.
2. Under aseptic conditions, the appropriate amount of vector was withdrawn from the stock vial(s) for a given patient treatment. As stated, this ranged from 1×10^6 pfu to 1×10^{11} pfu per treatment. The amount of vector administered to a given patient from treatment to treatment never varied.
3. After withdrawing the necessary amount of Ad-p53 from the stock vial(s), dilution in PBS for the purposes of administration, under sterile conditions, was performed (*see* **Subheadings 3.1.1.** and **3.1.2.**). **Step 4** of the protocol varied depending upon whether direct tumor injection or surgical bed administration of vector was performed. This is clarified below as the procedure for Ad-p53 administration for each delivery scenario is described.

3.1.1. Direct Tumor Injection of Ad-p53

For direct intratumoral administrations, Ad-p53 was diluted to a volume of PBS concordant with the number of tumor injections to be performed. Generally, we injected about 0.5 mL of vector solution at 1 cm (surface area) tumor increments. Thus, a very large tumor required the appropriate amount of vector to be diluted in a larger volume of PBS.

4. Injections were carried out by first passing the injection needle as far into the tumor as possible and injecting the vector solution slowly (*see* **Note 2**) as the needle and syringe were withdrawn. For the purposes of the first cycle, a tumor map was made so that subsequent Ad-p53 administrations during the cycle occurred in the exact locations as prior injections (**Fig. 1**). Hypopharyngeal, laryngeal, and cervical lesions were injected transcutaneously (*see* **Notes 3** and **4**). Oral cavity and oropharyngeal tumors were injected directly (*see* **Note 4**).

3.1.2. Intraoperative and Retrograde Catheter Administrations of Ad-p53 to the Tumor Bed

For these administrations, the appropriate amount of vector was always diluted to 10 mL in PBS.

5. At the completion of tumor extirpation, Ad-p53 was administered liberally (a "vector wash") to the tumor bed via a syringe and left in contact for 60 min prior to wound closure. Injections were performed along the margins of the resected neoplasms as well (**Fig. 2**). For the retrograde catheter administrations performed 72 h after surgery, the appropriate amount of Ad-p53 was also always diluted to 10 mL in PBS.

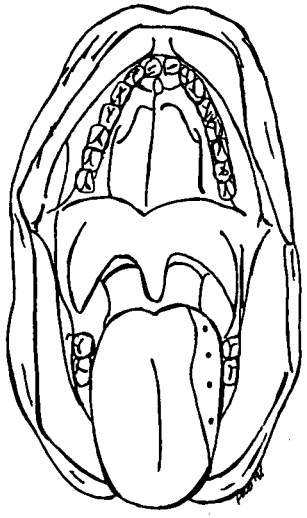

Fig. 1. Example of a typical tumor map for a left tongue carcinoma. Note incremental markings along left tongue lesion, indicating sites where Ad-p53 is injected.

6. Vector was administered via a syringe through the drains into the wound bed with clamps utilized to prevent efflux of the Ad-p53 for 1 h. The drains were subsequently removed in 24–48 h.

3.2. Patient Monitoring During Ad-p53 Administration

Because the treatment of SCCHN patients with Ad-p53 was within the context of a phase I clinical trial, patient monitoring for the detection of untoward effects and toxicities was quite stringent (*see* **Note 5**). All patients had vital signs, hematology, chest X-ray, blood chemistry, and performance status evaluated at the start of each treatment cycle. Patients were closely observed for a 2-h period following each treatment.

4. Notes

1. The healthcare workers with the greatest risk of Ad-p53 exposure had their serum and urine tested for the presence of infectious Ad-p53 and/or Ad-p53 DNA. All tests were negative. Low levels of anti-Ad-p53 antibody were detected in some serum samples, suggesting that no significant exposures to the adenovirus vector occurred.
2. To date, our clinical experience with the administration of Ad-p53 has been limited to patients with advanced recurrent SCCHN that had failed standard treatment modalities, including radiotherapy. This experience has been in the form of

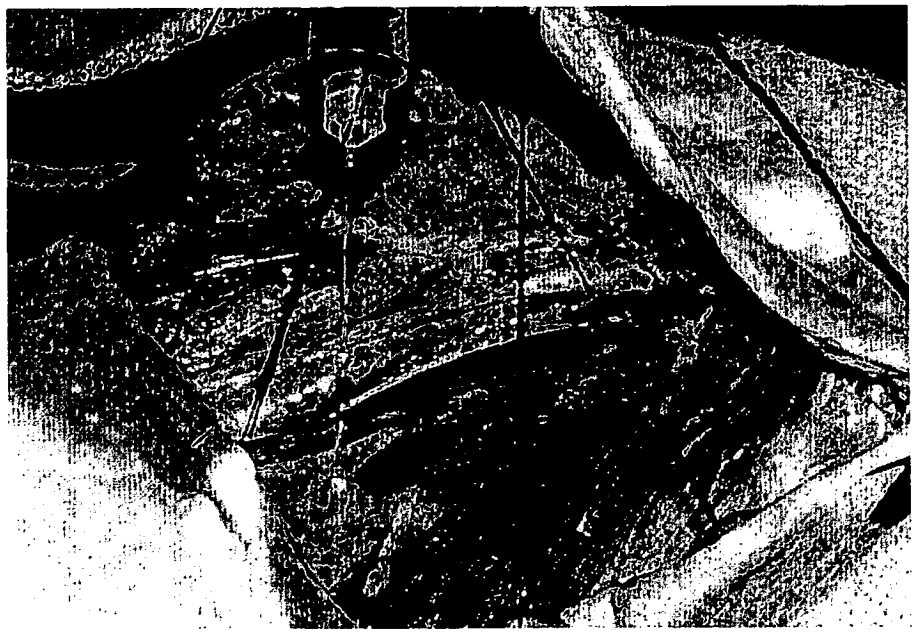

Fig. 2. Intraoperative delivery of Ad-p53 to tumor bed. Ad-p53 is being injected into the tumor margins subsequent to a "vector wash" of the tumor bed.

the clinical trial described. A consistent observation that has been made in the delivery of Ad-p53 to patients during the first cycle has been pain at the site of injection. It has been determined that this is secondary to the cold temperature of the recently thawed and diluted vector. It was initially thought that the Ad-p53 needed to be kept cold in order to preserve its infection ability. Stability studies suggest that the vector can be warmed to room temperature prior to patient injection. We anticipate that this may significantly diminish patient discomfort during administration.

3. Erythema at the site of injection was noted among several patients following transcutaneous injection of Ad-p53. This effect was never dose-limiting.
4. During the first cycle, it was not unusual for patients receiving higher viral doses per treatment ($1 \times 10^{9.5}$–1×10^{11}) to experience mild flu-like symtoms following Ad-p53 injections. These symptoms often extended through or recurred after the second treatment. Symptoms usually did not last into or beyond the third treatment of the first cycle. Flu-like symptoms could include all or only some of the following: Fever (as high as 39.4°C in one patient), sinus congestion, headache, and sore throat. Flu-like symptoms were never dose-limiting in our phase I experience.

5. Determining the patient biological distribution of Ad-p53 after administration was an important aspect of the phase I clinical trial. Patient blood, urine, and upper-aerodigestive tract secretions were assayed for the presence of Ad-p53 by a cytopathic effect assay (CPE) and Ad-p53 specific PCR. Although the technical details of the performance of these assays is beyond the scope of this chapter, it is important to point out that Ad-p53 was detected in blood and urine at higher vector concentrations. Vector quickly disappeared from blood within 24 h after a treatment. At high doses, vector could be detected in the urine of patients throughout treatment. The presence of vector in the urine ultimately disappeared within 3–17 d after the last Ad-p53 administration. As with blood and urine, Ad-p53 could also be detected in the sputum of patients after treatment at the higher doses, and would be present throughout a cycle. Ad-p53 would usually be cleared from the sputum within a week.

Acknowledgments

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Direct DNA Injection (*p53*) into HCC Tumors

Ragai R. Mitry and Nagy A. Habib

1. Introduction

Liver tumors, specially HCC, are among the most common malignancies in the world, and their annual world incidence is about 250,000 cases, with a male to female ratio 4 : 1 *(1)*. HCC is one of the most important neoplasms in tropical and subtropical regions, particularly among the sub-Saharan African black population and ethnic Chinese *(2)*. The prognosis is very poor, and patients with advanced tumors are unlikely to survive 3 mo *(3)*. Most HCC cases are beyond radical resection when detected. All other forms of the currently available therapies are rarely beneficial *(2)*.

Methods for modern molecular genetics have been developed to allow transfer and expression of foreign DNA sequences in human somatic cells and make human gene therapy possible *(4)*. In fact, gene therapy has altered the conventional path for cancer research. It offers the potential for developing innovative treatments for both inherited monogenic diseases like cystic fibrosis, and polygenic disorders such as cancer *(5)*. Various gene delivery systems are available including nonviral "naked" DNA or liposome/DNA complexes and viral retroviruses and adenoviruses.

Direct injection of naked DNA is a method that involves the direct injection of pure plasmid DNA into the desired tissue *(6)*. It is inexpensive and considered as one of the safest gene transfer techniques. The mechanism of naked DNA uptake by cells/tissues in vivo is not very clear, but the possible mechanisms involved are pinocytosis and endocytosis. In 1990, Wolff et al. injected β-galactosidase (*lacZ*) reporter gene DNA constructs into mouse skeletal muscles and showed that the *lacZ* expression was at significant levels *(7)*.

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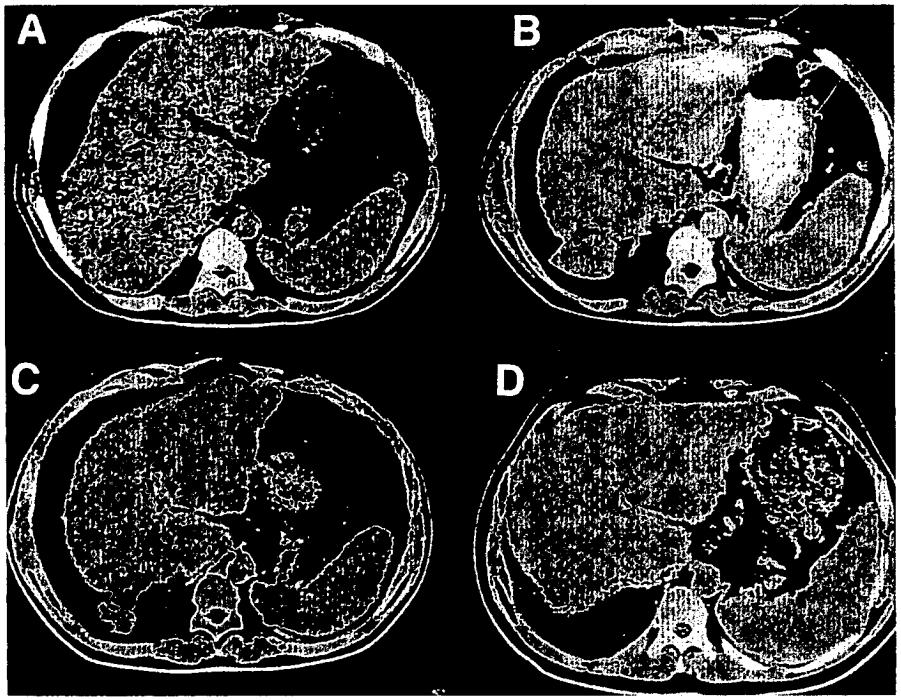

Fig. 1. CT scans of one of the HCC patients that have undergone wt-*p53* gene therapy. **(A)** Unenhanced CT scan case 4 prior to therapy. A 12-cm diameter tumor is seen in the posterior position of the right lobe of liver (AFP 1900 IU/L). **(B)** Contrast-enhanced CT scan of the same patient 3 mo later after two intratumoral injections of wt-*p53* shows a considerable reduction in size of the tumor, which now measures 5 cm in diameter (normal AFP). **(C)** Contrast-enhanced CT scan of same patient 6 mo after the commencement of therapy. The tumor now measures 2 cm in diameter (normal AFP). **(D)** Contrast-enhanced CT scan of the same patient 19 mo after the commencement of therapy. No tumor is seen (normal AFP).

In 1996, Habib and colleagues published the results of a pilot study carried out on five HCC patients, to assess the therapeutic potential of percutaneous injection of naked wild-type *p53* plasmid DNA, pC53-SN3 (wt-*p53*). The results showed objective tumor response in three of the five patients with reduction of the tumor volume (75, 90, and 95%) on computed tomographic (CT) scan measurements (**Fig. 1**) as well as a significant fall of serum α-fetoprotein (AFP). No mortality or morbidity owing to the injections *(8)*. The procedures used in that study are explained in details in the methods section.

2. Materials

1. Bacterial resuspension buffer: 50 m*M* glucose, 25 m*M* Tris-HCl (pH 8.0), 10 m*M* EDTA (pH 8.0) and autoclave.
2. Bacterial lysis buffer: 0.2 *N* NaOH, 1% SDS.
3. Bacterial neutralisation buffer: 60 mL of 5*M* potassium acetate, 11.5 mL glacial acetic acid, 28.5 mL ddH_2O.
4. Lauria-Bertani (LB) broth: 10 g NaCl, 5 g Bacto-yeast extract, 10 g Bacto tryptone, 2 mL 1*M* NaOH, add distilled H_2O to make up 1000 mL and autoclave.
5. LB agar plates: 0.7% agar in LB broth (w/v), then autoclave.
6. Ampicillin: 50 mg/mL dissolved in sterile ddH_2O and filtered through a 0.2-μm filter; stored as small aliquots.
7. *Escherichia coli* (XL-1 Blue) purchased from Stratagene (La Jolla, CA) and processed according to the manufacturer's instructions. The bacteria is then stored at –80°C as 100-μL aliquots in sterile 0.5-mL microfuge tubes.
8. Tris-EDTA buffer (TE): 10 m*M* Tris base, pH 7.5, 1 m*M* EDTA (disodium salt).
9. Phosphate-buffered saline (PBS): 2.3 g anhydrous Na_2HPO_4, 0.59 g $NaH_2PO_4.2H_2O$, 18 g NaCl. Add distilled H_2O to make 2000 mL. pH should be ~7.3.
10. Lysis buffer: 0.32*M* sucrose, 10 m*M* Tris base, pH 7.5, 5 m*M* $MgCl_2$, 1% (w/v) Triton-x100.
11. 10% SDS in ddH_2O.
12. Proteinase K solution: proteinase K dissolved in autoclaved 0.075*M* NaCl, 0.024*M* EDTA, pH 7.5 at a concentration of 10 mg/mL.
13. Sodium acetate (NaAc): 3*M*, pH7.0.
14. Phenol/Chloroform mixture: 1:1 ready mixed (purchased from Sigma-Aldrich). This mixture is TOXIC and should be handled with gloves in fume cupboard.
15. Choloroform.
16. Absolute alcohol (ethanol).
17. 70% ethanol: diluted in ddH_2O.
18. DNA *Taq* polymerase enzyme.
19. KCl, 10X *Taq* polymerase buffer (supplied with the DNA *Taq* polymerase enzyme).
20. Deoxnucleotide triphosphates mixture (dNTP's): 1.25 m*M* dATP, 1.25 m*M* dCTP, 1.25 m*M* dGTP, 1.25 m*M* dTTP.
21. Loading buffer: 40% sucrose, 0.025% w/v bromophenol blue, 0.025% w/v xylene cyanol.
22. Ethidium bromide (EtBr) solution: 10 mg dissolved in distilled H_2O. HIGHLY TOXIC, handle with care. Store in a dark bottle at 4°C.
23. 10X TBE running buffer: 890 m*M* Tris-HCl, pH 8.0, 890 m*M* boric acid, 200 m*M* EDTA (disodium salt).
24. Fixation solution: 2% formaldehyde, 0.2% glutaraldehyde, in PBS.
25. X-gal substrate solution: 5 m*M* potassium ferricyanide, 5 m*M* potassium ferrocyanide, 2 m*M* magnesium chloride, in PBS.

Store SDS, NaAc solutions, chloroform, absolute alcohol, and bacterial lysis buffer at room temperature (RT). Store DNA template(s), loading buffer, lysis buffer, LB broth, LB agar plates, bacterial resuspension buffer, and bacterial neutralization buffer, in a refrigerator or cold room (4°C). Other solutions should be stored at –20°C.

3. Methods

3.1. Preparation of Plasmid DNA

3.1.1. E. coli Cultures Transformation and Glycerol Stock Preparation

Plasmids are introduced into *E. coli* by a process know as transformation. This process can be used for any plasmid. The transformed bacteria are then selected twice on Lauria-Bertani agar plates containing the appropriate antibiotic. For example, in the following procedure, the antibiotic used is ampicillin. Small LB liquid cultures are then prepared and used for preparation of glycerol stocks of the transformed bacteria. Note that all the following steps should be carried out close to a flame.

1. Defrost a 100-µL *E. coli* aliquot on ice.
2. Flame mouth of the tube containing the bacteria then using a sterile loop and close to the flame, introduce a small quantity of the plasmid (dissolved in TE) onto the bacteria by dipping the loop into the *E. coli* aliquot. Recap the tube and mix contents by gentle shaking. Centrifuge tube briefly (pulse centrifugation) in a microfuge then place on ice for 30 min.
3. Close to the flame and using a sterile tip, transfer the bacterial aliquot onto an LB agar plate containing ampicillin. Using a sterile loop or glass spreader, spread the bacteria on the surface of the agar.
4. Incubate the plate overnight at 37°C. The next day, using a sterile loop, pick a single well isolated colony and spread it on another fresh LB agar plate/ampicillin. Incubate plate overnight at 37°C. Seal the first plate using "para-film" and place in the refrigerator for up to 1 mo.
5. The following day, in two sterile universal tubes (10-mL sample tubes), place 5 mL LB broth in each. Add 5 µL of ampicillin stock solution and using a sterile loop, transfer a well isolated colony from the plate to each of the two tubes. Recap tubes and mix the contents by vigorous shaking, then place in a shaking incubator, overnight at 37°C. Seal the plate and store in fridge.
6. The following cultures should be turbid because of bacterial growth. Label two "cryo-tubes" with the name of the plasmid and date. Close to a flame, place 1.5 mL of culture in corresponding cryo-tube, then add 300 µL glycerol. Recap the cryo-tubes and mix contents by inversion (6–7 times). Store tubes in –80°C. Part of the remaining 3.5 mL of the culture will be used in confirmatory tests (**Subheadings 3.1.2.** and **3.2.5.**).

3.1.2. Confirmation of Successful Transformation

Subheading 3.1.1., steps 3 and **4**, confirm that transformation was successful because the *E. coli* was able to grow on plates containing an antibiotic, i.e., the bacteria became resistant. A more reliable way for confirmation of successful transformation would be restriction enzyme (endonuclease) digestion. The supplier of the plasmid(s) should provide a schematic map for the plasmid, which would show the insertion site (cloning site) of the gene of interest, e.g., wt-*p53*. Also, this map would show the restriction enzyme sites that could be used to confirm the "structure" of the plasmid. For example, *Bam*HI (**Fig. 2**) could be used to digest the wt-*p53* plasmid (8.4 kb in length) resulting in two DNA fragments of 1.8 kb of wt-*p53* gene and 6.6 kb of vector.

1. Transfer 1.5 mL of each LB culture into a microfuge tube (1.5-mL or 2-mL tube), and centrifuge tubes at high speed for 1.5 min.
2. Carefully remove supernatant and centrifuge tubes for few seconds, then remove any remaining traces of supernatant.
3. Using a vortex, resuspend pellet in 150 µL of bacterial resuspension buffer.
4. Add 150 µL bacterial lysis buffer and mix contents by gently inverting the tube (6–7 times). Do not vortex.
5. Add 150 µL neutralisztion buffer and mix contents by inverting the tube (about 10 times), followed by centrifugation at a high speed and 4°C for 5 min.
6. Carefully and without disturbing the pellet, transfer the supernatant into a fresh microfuge tube. Precipitate the plasmid DNA by adding 1.0 mL ice-cold absolute alcohol. Mix by inverting the tubes about 10 times.
7. Centrifuge tube at high speed and 4°C for 5 min. Then remove supernatant and remove all traces of the supernatant.
8. Let air-dry for about 2 min, then resuspend pellet in 40 µL TE by gentle tapping.
9. Transfer 20 µL plasmid solution into a fresh microfuge tube, then digest the sample with the appropriate restriction enzyme(s), (*see* **Subheading 3.2.5.**).
10. Prepare 0.8% agarose gel (*see* **Note 11**) and run samples of the undigested and digested plasmid, alongside a DNA marker ladder. Check for the presence of bands at the expected lengths. One band should appear in the lane of undigested plasmid and more than one band in the lane of digested plasmid depending on the enzyme(s) used (*see* **Fig. 2**) and number of sites.

3.1.3. Plasmid Extraction and Sterilization

3.1.3.1. Plasmid Extraction

Commercially available plasmid extraction kits are reliable and easy to use. The kits used in the pilot study carried out by Habib et al. *(8)*, were purchased from Qiagen Ltd., Chatsworth, CA. The following steps will explain the preparation of large cultures required for use with any plasmid extraction kit or protocol.

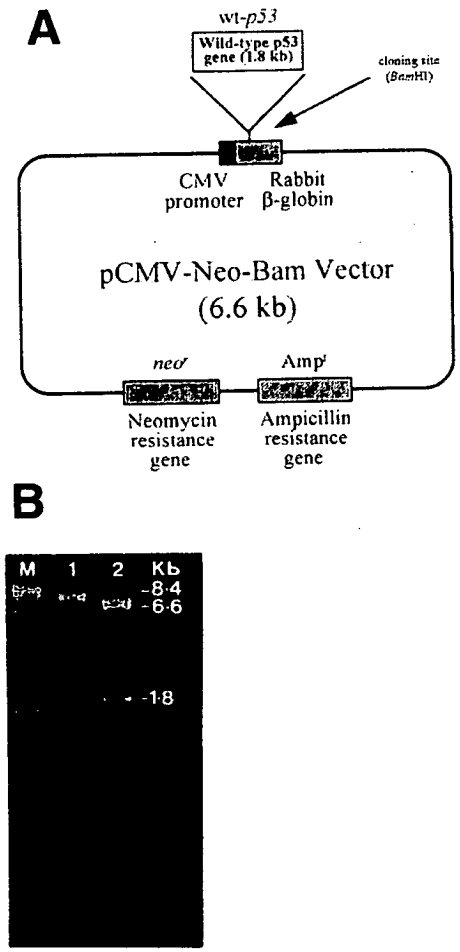

Fig. 2. (**A**) A schematic of pC53-SN3 plasmid, and (**B**) *Bam*HI restriction (endonuclease) enzyme digestion of pC53-SN3 plasmid. Lane M: 1 kb DNA markers ladder; lane 2: plasmid before digestion, and lane 3: plasmid after digestion.

1. In sterile universal tubes, place 10 mL LB broth per tube, then add 10 µL ampicillin stock solution. Using a sterile loop, transfer a "pinch" of the bacterial glycerol stock into each of the tubes. Recap tubes and mix contents by vigorous shaking, then place in a shaking incubator overnight, at 37°C. The contents of each tube will be used to seed 250–500 mL LB broth.
2. The following day, use 2 L sterile conical glass flasks to prepare large cultures. The number of flasks used will depend on the amount of plasmid to be prepared and kit used. Use 500 mL LB broth per flask. Add 500 µL ampicillin stock solution, followed by a single 10-mL culture from **step 1**. Recap the flasks and incubate flasks in a shaking incubator (200–250 throws per min) overnight, at 37°C.
3. Pellet the bacterial cells in large centrifuge bottles. The speed of centrifugation will depend on the bottles type and the plasmid extraction protocol used. Follow the instructions supplied with the extraction kit.
4. Dissolve the plasmid in TE. The volume depends on the expected amount of extracted plasmid. The final plasmid concentration should be ≥ 1 µg/µL.
5. The final product can be analysed using the restriction enzyme digestion technique (**Subheading 3.2.5.**).

3.1.3.2. Plasmid Sterilization

The following procedure must be carried out in a class II laminar flow cabinet.

1. Determine the exact plasmid DNA concentration using a spectrophotometer set for UV absorption at 260 nm. For example, dilute 10 µL concentrated plasmid in TE to a total volume of 1 mL. A reading of 1 corresponds to 50 µg of DNA (plasmid or genomic). Work out the original concentration of the undiluted solution.
2. In the laminar flow cabinet, dilute the plasmid using sterile TE to give a final concentration of about 1 µg/mL. Using a sterile disposable syringe, filter the solution through a sterile 0.2-µm filter in a sterile universal tube. Repeat the filtration step. At this point, the sterilized solution can be stored at 4°C until use.
3. Samples of the sterilised plasmid should be tested for bacterial, viral, and mycoplasma contamination.

3.2. Patients and Treatment with wt-p53 Naked Plasmid DNA

3.2.1. Patients

1. Confirm malignancy histologically.
2. Perform CT scan before and after treatment. Monitoring of tumor size is always reported on the injected lesion. Also monitor the appearance and progress of other untreated lesion(s), if present.
3. Check the level of one of the appropriate tumor markers before and after treatment. For example in case of HCC patients, use serum AFP.
4. Prior to and following the wt-*p53* injections, all patients should have: full blood count, serum electrolytes, urea, creatinine, liver function, and coagulation profiles.
5. On the day of treatment, specially postinjection, all patients should be monitored for pulse, blood pressure, central venous pressure, urine output, and body temperature.
6. Patients should sign a consent form. This form should explain the nature of the procedures, the risks involved, and the unproven results of this therapeutic approach.

7. Most of the patients would be discharged on the same day of the procedure. The complications that may be observed include transient fever, hypotension, or hypertension. These side effects are expected to last for about 2 h and usually cease without treatment. Some patients might require hospitalization for 24 h.

3.2.2. Therapeutic Protocol

1. The first injection would be a single injection of 2 mg naked wt-*p53* plasmid DNA.
2. Inject plasmid percutaneously and intratumorally under CT scan.
3. Consider 50% reduction in serum AFP level and 50% diminution of tumor volume post-treatment, as a positive response. When estimating the volume of tumor, always use the greater diameter measured on CT scan.
4. Patients showing positive response or stable disease could be offered further injections at monthly intervals.
5. Two core biopsies of the treated lesion ~36 h postinjection could be analyzed for gene transfer and expression. Immediately place each biopsy in a labeled cryo-tube and snap-freeze in liquid nitrogen. At this point, the biopsies could be stored in a –80°C freezer or processed for DNA and/or RNA extraction. Make use of the marker gene(s) of the plasmid, e.g., *neo*^{r} or *lacZ*.

3.2.3. Use of lacZ as a Marker Gene and β-galactosidase Activity Analysis

The genes of interest (e.g., *p53*) could be obtained already cloned in vectors that express *lacZ* marker gene, other than the antibiotic resistance genes. Well-established molecular biology laboratories could be asked to clone the gene of interest into a vector that expresses the *lacZ* gene.

1. Thirty-six h postinjection, a core biopsy of the treated lesion is obtained and split into two halves. One half is placed in a cryo-tube and immediately snap-frozen in liquid nitrogen. This sample could be analyzed biochemically for β-galactosidase activity using a commercially available β-galactosidase assay kits or published protocols. The other half is immediately processed for histochemical analysis (*see* **steps 4–8**).
2. Cut 5-μm frozen sections in the specimens. These sections are then stained using the chromogenic substrate X-gal (*9*).
3. On each tissue section, place 100 μL of fixation solution and incubate for 10 min at RT.
4. Remove fixation solution, then wash sections by placing 300 μL PBS, for 2 min at RT, then discard PBS. Repeat the washing step twice.
5. Remove traces of PBS around the sections using a filter paper.
6. Place the slides on 3–4 layers of water-moistened filter paper inside a "lunch box." Place 100 μL X-gal staining solution on each section and cover the box with the lid. Gently place the box in an incubator at 37°C for 4–5 h.

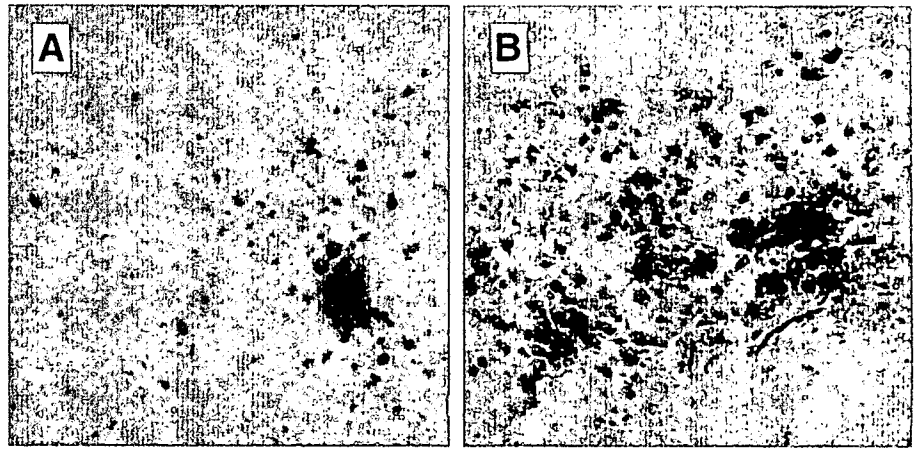

Fig. 3. Histochemical detection of β-galactosidase activity in 5-μm frozen sections in HCC tumors grown subcutaneously in nude mice. Thirty-six h posttreatment **(A)** control tumors injected with buffer and **(B)** tumors injected with a single dose of 50 μg of naked β-gal plasmid DNA. The sections were counter-stained with light haematoxylin and eosin.

7. Remove the staining solution. Gently and briefly, dip sections in PBS (in a beaker).
8. The sections are ready to be counter-stained with light haematoxylin/eosin. Then examine the sections under a light microscope (×100 or ×200 magnification). The cells showing high activity of β-galactosidase activity will stain blue (**Fig. 3**). The percentage of blue-stained cells can be worked out. In fact, if nontumor biopsies are processed/stained in the same way, you might not see any blue-stained cells in the section because all the cells should have low enzymatic activity.

3.2.4. DNA Extraction

1. Crush the frozen tissue specimen inside the cryo-tube using a sterile glass rod. Split the crushed tissue into two equal parts and store one part at –80°C which will be used in RNA extraction. Process the other part as follows.
2. Add 0.5 mL lysis buffer (containing 0.5% SDS per mL). Add 100 μg proteinase K per mL and recap the tubes. Place tubes in a shaking incubator (gentle shaking, about 70–80 throws per minute) at 37°C overnight.
3. Transfer the digested sample into a fresh sterile 1.5-mL microfuge tube. Add equal volume of phenol:chloroform and 1/10 volume NaAc and mix contents using a roller or gyratory shaker for 15 min, at RT.
4. Centrifuge tubes at 7000*g* and RT for 10 min, then carefully, without disturbing interface layer, transfer the top aqueous layer into a fresh microfuge tube.
5. Add equal volume of phenol:chloroform and mix on a shaker for 15 min at RT.

6. Repeat **steps 4** and **5** until no interface layer is visible. Finally, transfer the aqueous layer into a fresh microfuge tube.
7. Precipitate DNA by adding an equal volume of ice-cold absolute alcohol and mix by inversion (about 10 times), then place in –20°C freezer overnight. At this point, tubes can be stored in freezer for several months.
8. If DNA is required, then centrifuge tubes at 7000*g* and 4°C for 10 min. Discard supernatant, then resuspend DNA pellet in 0.5 mL 70% alcohol.
9. Transfer the suspension into a sterile 1.5-mL microfuge tube and centrifuge at 7,000*g* and RT for 10 min.
10. Discard supernatant and let pellets air-dry for 2–3 min, then resuspend each pellet in 0.5 mL TE. Resuspension could be done by gentle tapping. Place tubes in the refrigerator to allow DNA to dissolve slowly.

3.2.5. Restriction Enzyme Digestion of DNA

1. Place ~5 µg DNA sample (plasmid DNA, genomic DNA, and PCR product) in a microfuge, then add: 4 µL 10X buffer (supplied with enzyme), 20 U restriction enzyme. Add ddH_2O to make up total volume to 40 µL, then mix contents by gentle tapping.
2. Centrifuge tube for 1 s (pulse centrifugation), then place the tubes at the appropriate optimal temperature for the enzyme used for about 4 h. Sometimes a longer period of incubation is required. In fact, to ensure that digestion is complete, the tubes could be incubated overnight.
3. Analyze samples of undigested and digested DNA agarose gel electrophoresis alongside a DNA marker ladder. Prepare agarose gel of appropriate percentage, depending on the length of the DNA fragments.

3.2.6. Use of neo^r as a Marker Gene

Tumor biopsies can be analyzed for exogenous gene transfer and expression by using the neomycin resistance gene as a marker gene.

3.2.6.1. Detection of Gene Transfer Using PCR Technique

Ensure that all diposable tips, tubes and plasticware, and solutions used are sterile. Use fresh tips when pipeting the various solutions and samples. The following protocol is used with a thermocycler (PCR machine) that does not require mineral oil to be placed on top of reaction mixture. If mineral oil is required, then carefully and gently place a drop of the oil on the surface of reaction mixture in each tube.

1. Dilute each DNA sample in sterile ddH_2O to a final concentration of ~25 ng/µL. Place 10 µL sample in the reaction tube.
2. In a sterile 1.5-mL microfuge tube, prepare sufficient "master mix" solution for the samples to be analyzed. For example: 5 µL 10X reaction buffer, 8 µL dNTP's mixture, 1 µL primer1, 1 µL primer2, ~24.5 µL sterile ddH_2O, ~2 U *Taq* polymerase (~0.5 µL, depending on the concentration of the polymerase). Mix contents of tube by gentle tapping, followed by brief centrifugation.
3. Add 40 µL master mix to each DNA sample. A negative control tube can be included in which 10 µL sterile ddH_2O are used instead of DNA. Gently triturate samples (mixing sample by up/down pipeting). Cap the tubes and place in PCR machine and start the run. For example, to detect a 791 bp fragment of *neo^r* (**Fig. 4**), the following primers ***(10)*** and PCR cycles could be used:
   primer1 (forward): 5′ CAA GAT GGA TTG CAC GCA GG 3′
   primer2 (reverse): 5′ CCC GCT CAG AAG AAC TCG TC 3′
   PCR cycles: 1X cycle 5 min at 94°C
   30X cycles 1 min at 94°C (denaturing)
   2 min at 64°C (annealing)
   3 min at 72°C (extension)
   1X cycle 7 min at 72°C
4. The final product can be stored at 4°C until analyzed, or samples of the PCR products and their *Pst*I restriction enzyme digestion products could be analyzed on a 1% agarose gel (**Fig. 5**).

3.2.6.2. Detection of Gene Expression Using RT-PCR Technique

Reverse transcriptase polymerase chain reaction (RT-PCR) can be used to find out if a gene has been expressed or not. Many commercially available kits could be used to carry out RT-PCR. Most of these kits are easy to use and reliable. This technique involves the extraction of messenger RNA (mRNA) from cells/tissue using, e.g., Micro-FastTrack mRNA Isolation Kit (Invitrogen, San Diego, CA) and reverse transcribe it into complementary DNA (cDNA) using, e.g., cDNA Cycle Kit (Invitrogen).

1. Extract mRNA from treated and control tissues.
2. Reverse transcribe the mRNA into cDNA.
3. Analyze samples of the cDNA using the *neo^r* PCR primers (**Subheading 3.2.6.1.**).
4. Digest samples of the PCR products using *Pst*I restriction enzyme.
5. Analyze the PCR and digestion products on agarose gel (**Fig. 5**).
6. The results should show if there is gene expression or not.

4. Notes

1. All buffers/solutions are prepared in deionised distilled water (ddH_2O) and autoclaved wherever appropriate.
2. Dissolve SDS by slow mixing in order to avoid foaming. Do not attempt to autoclave SDS solution, as autoclaving leads to foaming. SDS precipitates at low temperature or if placed in fridge by mistake. If precipitate is formed, warm up the solution under running hot water or by brief microwaving.
3. All tubes and disposables must be sterilized by autoclaving wherever appropriate or purchased ready sterile.

```
5'ACAGCAAGCGAACCGGAATTGCCAGCTGGGGCGCCCTCTGGTAAGGTTGGGAAGCCCTGCAAAGTAAACTGGATGGCT
TTCTTGCCGCCAAGGATCTGATGGCGCAGGGGATCAAGATCTGATCAAGAGACAGGATGAGGATCGTTTCGCATGATTGA
ACAAGATGGATTGCACGCAGGTTCTCCGGCCGCTTGGGTGGAGAGGCTATTCGGCTATGACTGGGCACAACAGACAATCG
GCTGCTCTGATGCCGCCGTGTTCCGGCTGTCAGCGCAGGGGCGCCCGGTTCTTTTTGTCAAGACCGACCTGTCCGGTGCC
CTGAATGAACTGCA▼GGACGAGGCAGCGCGGCTATCGTGGCTGGCCACGACGGGCGTTCCTTGCGCAGCTGTGCTCGAC
GTTGTCACTGAAGCGGGAAGGGACTGGCTGCTATTGGGCGAAGTGCCGGGGCAGGATCTCCTGTCATCTCACCTTGCTCC
TGCCGAGAAAGTATCCATCATGGCTGATGCAATGCGGCGGCTGCATACGCTTGATCCGGCTACCTGCCCATTCGACCACC
AAGCGAAACATCGCATCGAGCGAGCACGTACTCGGATGGAAGCCGGTCTTGTCGATCAGGATGATCTGGACGAAGAGCAT
CAGGGGCTCGCGCCAGCCGAACTGTTCGCCAGGCTCAAGGCGCGCATGCCCGACGGCGAGGATCTCGTCGTGACCCATGG
CGATGCCTGCTTGCCGAATATCATGGTGGAAAATGGCCGCTTTTCTGGATTCATCGACTGTGGCCGGCTGGGTGTGGCGG
ACCGCTATCAGGACATAGCGTTGGCTACCCGTGATATTGCTGAAGAGCTTGGCGGCGAATGGGCTGACCGCTTCCTCGTG
CTTTACGGTATCGCCGCTCCCGATTCGCAGCGCATCGCCTTCTATCGCCTTCTTGACGAGTTCTTCTGAGCGGGACTCTG
GGGTTCGAAATGACCGACCAAGCGACGCCCAACCTGCCATCACGAGATTTCGATTCCACCGCCGCCTTCTATGAAAGGTT
GGGCTTCGGAATCGTTTTCCGGGACGCCGGCTGGATGATCCTCCAGCGCGGGGATCTCATGCTGGAGTTCTTCGCCCACC
CCGGGCTCGATCCCCTCGCGAGTTGGTTCAGCTGCTGCCTGAGGCTGGACGACCTCGCGGAGTTCTACCGGCAGTGCAAA
TCCGTCGGCATCCAGGAAACCAGCAGCGGCTATCCGCGCATCCATGCCCCCGAACTGCAGGAGTGGGGAGGCACGATGGC
CGCTTTGGTCGACCCGGACGGGAC 3'
```

P1

PstI digestion site

P2

Fig. 4. The neomycin resistance gene sequence. Obtained from the database at European Molecular Biology Laboratory (EMBL) through the World Wide Web. P1: sequence of forward primer, Primer1; P2: complementary sequence to reverse primer, Primer2.

Fig. 5. An example for PCR amplification products of *neo*^{r} gene, analyzed on 1% agarose gel. Control samples (lane 1: DNA and lane 3: cDNA) and treatment samples (lane 2: DNA and lane 4: cDNA). Lane 5: pC53-SN3 DNA sample as positive control for *neo*^{r}. Lane 6: *Pst*I digestion products.

4. Defrost all solutions/mixtures required for PCR reactions at RT. During use, place defrosted solutions/mixtures on ice until ready to place back in freezer. Always keep the *Taq* polymerase in the freezer until it is required to be added to PCR reaction, then immediately place back in freezer.
5. Preparation of agar plates: place 100 mL LB broth in an autoclavable glass bottle, then add 0.7 g agar and sterilize by autoclaving. Allow to cool to ~45°C, then add the appropriate amount of antibiotic and mix contents by gentle shaking. Close to a flame pour about 20–25 mL molten agar/LB into each 10-cm Petri dish. Allow plates to set (cool to RT), then place dishes upside down in an incubator overnight at 37°C. The following day, label the dishes on the bottom surface with the antibiotic's name. Seal dishes with parafilm and store in the refrigerator until use.
6. Bacterial plates should be clearly labeled on bottom surface with the full name of the plasmid and date because you may need to use them again, if the small cultures (5 mL) were not successful.
7. X-gal stock solution is colorless. Discard solution if it shows a light pink coloration.
8. Always keep a bottle of absolute alcohol (about 200 mL) in −20°C freezer, required for the DNA precipitation.
9. Formalin-fixed tumor biopsies pre- and posttreatment could also be analyzed immunohistochemically for *p53* activity.
10. The endotoxin (lipopolysaccharides) level in the final plasmid product obtained using Qiagen kits is usually less than the level set by the FDA. Endotoxin-free plasmid extraction kits are commercially available, e.g., from Qiagen.
11. Preparation of agarose gel: place the appropriate volume of 1X TBE in a conical flask and add the agarose (weight depends on % required). Microwave for about 1–2 min and let stand until temperature is about 50°C. Add 0.5 µL of EtBr per 10 mL of prepared gel. Gently swirl the mixture. Pour mixture into the casting "boat," insert comb and let stand at RT for ~45 min. Place sample(s) in fresh microfuge tube(s), add half volume of loading buffer and mix by gentle tapping. Carefully, remove comb and place gel in the electrophoresis tank. Pour 1X TBE

on gel until its level about 2–3 mm above surface of gel, ensuring that there are no air bubbles trapped in wells. Place samples in the wells. The amount of sample depends on tooth width of comb used. Load 1 µL sample (PCR or digestion products) per mm of tooth width.
12. Change gloves often and use freshly sterilized microfuge tubes, disposables, and solutions/ddH_2O as contamination is possible especially with PCR/RT-PCR work.
13. Disposing EtBr and cleaning contaminated/spillage areas are carried out according the regulations and rules set by the senior staff in charge of the laboratory.
14. If dark bottles are not available, wrap the tube or bottle in alimunium foil. Do not forget to label both the bottle and the wrapper.

Acknowledgments

We thank Dr. Bert Vogelstein for kindly providing the wt-*p53* plasmid.

R ferences

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A Phase II Trial of Intratumoral Injection with a Selectively Replicating Adenovirus (ONYX-015) in Patients with Recurrent, Refractory Squamous Cell Carcinoma of the Head and Neck

David H. Kirn

1. Introduction

Selectively replicating viruses may offer a new approach to cancer treatment. If successful in clinical trials, these agents will constitute a new category in the antitumoral armamentarium. Many viruses are currently being studied, and an adenovirus (ONYX-015) first entered clinical trials in 1996; herpesvirus agents are scheduled to enter clinical trials in 1998. Critical issues need to be addressed if the utility of these agents is to be optimized. For each virus, the effect of antiviral immunity on antitumoral efficacy must be better understood. For all viruses, physical barriers to spread within tumors (e.g., fibrosis, pressure gradients) must be overcome. Although proof-of-concept experiments with chemotherapy and ONYX-015 have been encouraging, further studies are required to determine optimal treatment-regimen sequencing. Combination studies with radiation therapy are also underway with ONYX-015. Finally, these agents may require modification (e.g., coat modification) in order to maximize effectiveness against systemic metastases following intravenous administration.

1.1. Preclinical Development of ONYX-015

p53 is mutated in roughly 50% of all human cancers, including nonsmall cell lung (60%), colon (50%), breast (40%), head and neck (60%), and ovarian (60%), cancers in the advanced stages. Loss of *p53* function is associated with

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resistance to chemotherapy and/or decreased survival in numerous tumor types, including breast, colon, bladder, ovarian, and nonsmall cell lung cancers. Therefore, effective therapies for tumors that lack functional *p53* are clearly needed.

p53 mediates cell cycle arrest and/or apoptosis in response to DNA damage (e.g., owing to chemotherapy or radiation) or foreign DNA synthesis (e.g., during virus replication). Consequently, DNA tumor viruses such as adenovirus, SV40, and human papilloma virus encode for proteins that inactivate *p53* and thereby allow efficient viral replication. For example, the adenovirus E1B-region 55 kD protein binds and inactivates *p53*, in complex with the E4orf6 protein. Because *p53* function must be blocked in order to allow efficient virus replication, Dr. Frank McCormick hypothesized that an adenovirus lacking E1B, 55 kDa gene expression might be severely limited in its ability to replicate in normal cells; however, cancer cells that lack *p53* function should support virus replication and resultant cell destruction. ONYX-015 (ONYX Pharmaceuticals, Richmond, CA) is an attenuated adenovirus type 2/5 chimera (dl1520) with two mutations in the early region E1B, 55 kDa gene; this virus was created in the laboratory of Dr. Arnie Berk *(1)*. The cytopathic effects of wild-type adenovirus and ONYX-015 were studied on a pair of cell lines that are identical except for *p53* function: the RKO human colon cancer cell line with normal *p53* function (the parent line), and an RKO subclone transfected with dominant-negative *p53* (courtesy of Dr. Michael Kastan) *(2)*. As predicted, ONYX-015 induced cytopathic effects identical to wild-type adenovirus in the subclone lacking functional *p53*, whereas cytopathic effects with ONYX-015 were reduced by approximately two orders of magnitude in the parental tumor line harboring normal *p53*. Subsequently, a tumor cell line that was resistant to ONYX-015 because of normal *p53* function (U2OS), became sensitive to ONYX-015 following transfection and expression of the E1B, 55 kDa gene. Therefore, ONYX-015 is able to replicate selectively in *p53*-deficient cancer cells resulting from a deletion in the E1B, 55 kDa gene.

Subsequent experiments demonstrated that primary (nonimmortalized) human endothelial cells, fibroblasts, small airway cells, and mammary epithelial cells highly resistant to ONYX-015 replication and cytolysis, in contrast to effects seen with wild-type adenovirus *(3)*. Replication-dependent cytopathic effects were demonstrated in human tumor cell lines of many different histologies following infection with ONYX-015. Tumor cells that lack *p53* function through different mechanisms (*p53* gene mutation and/or deletion, or *p53* degradation by human papilloma virus E6 protein) were shown to be destroyed by ONYX-015. In addition, several carcinoma lines with normal *p53* gene sequence, including two chemotherapy-resistant ovarian cancer subclones,

were efficiently lysed. ONYX-015 had significant in vivo antitumoral activity against subcutaneous (sc) human tumor xenografts in nude mice following intratumoral or intravenous injection. The in vivo efficacy against each tumor type correlated with the in vitro sensitivity of the cell line to ONYX-015. Efficacy against intraperitoneal (ip) carcinoma was documented following ip virus administration (C. Heise and D. Kirn, publication pending). Because of the lack of efficient replication in rodent cells, however, immunocompetent (syngeneic) tumor models have not been useful for studying replication-dependent effects. Therefore, the role of the antiviral and antitumoral immune responses may only be determined in cancer patients until a novel model is developed.

2. Clinical Development of ONYX-015

ONYX-015 is a novel agent with a novel mechanism of action *(3)*. We predicted that both toxicity and efficacy would be dependent on the intrinsic ability of a given tumor to replicate the virus, to the location of the tumor to be treated (e.g., intracranial vs peripheral), and to the route of administration of the virus. In addition, data on viral replication, antiviral immune responses, and their relationship to antitumoral efficacy were critical in the early stages of development. We, therefore, elected to treat patients with recurrent head and neck carcinomas initially.

2.1. Phase I Trial: Head and Neck Cancer

The rationale for targeting this population as follows. These tumors are frequently amenable to direct injection and biopsy in the outpatient clinic setting. *p53* abnormalities are very common; gene mutations or deletions are present in up to 70% of recurrent tumors *(4,5)*, and other *p53*-inactivating mechanisms such as mdm-2 overexpression and HPV E6 expression appear to be present in another 15–20% of these tumors. Finally, most patients suffer severe morbidity, and even mortality, from the local/regional progression of these tumors. Up to two-thirds of these patients die because of local complications. Therefore, a local therapy might lead to significant palliation and even survival prolongation.

Patients enrolled onto the phase I trial had recurrent squamous cell carcinoma of the head and neck that was not surgically curable and had failed either prior to radiation or chemotherapy *(6)*. *p53* gene sequence and immunohistochemical staining were determined on all tumors, but were not used as entry criteria. Other baseline tests included lymphocyte subsets (CD3, 4, 8), delayed-type hypersensitivity skin testing (including mumps and candida), and neutralizing antibodies to ONYX-015. This was a standard phase I dose escalation trial in which at least three patients are treated per dose level prior to escalation

to the next cohort; intrapatient dose escalation was not allowed. Six patient cohorts received single intratumoral injections of ONYX-015 every 4 wk (until progression) at doses from 10^7 to 10^{11} PFU per dose. Two additional cohorts received five consecutive daily doses of 10^9 or 10^{10} per day (total dose 5×10^9 or 5×10^{10}) every 4 wk. Following treatment, patients were observed for toxicity and for target (injected) tumor response. Additional biological end points included changes in neutralizing antibodies, the presence of virus in the blood (PCR days 3, 8), viral replication within the injected tumor (in tumor biopsies on days 8 and 22), and associated immune cell infiltration.

No significant toxicity was seen in any of the 32 patients treated. Eleven patients received repeat treatments (2–7 total). Grade 3 tumor site pain was noted on a single occasion in one patient. Otherwise, tumor-injection site pain was either nonexistent or mild. Flu-like symptoms were noted in approximately one-third of patients on the single-dose regimen and two-thirds of patients on the daily X 5 regimen. Symptoms included low grade fevers (less than 38.5°C), grade 1–2 myalgias and grade 1 nausea. Symptoms typically started within 12 to 24 h of injection and lasted for 1–5 d. Following ONYX-015-induced tumor necrosis, nonbleeding ulcerations developed over several injected tumors. However, no significant local complications occurred.

Neutralizing antibodies were positive in approximately 70% of the cases prior to treatment. Following treatment, all patients had positive antibody titers, and all patients had an increase in antibody titer. Replication was identified infrequently on day 8 tumor biopsies in patients on the single injection protocol, whereas day 8 biopsies were almost uniformally positive in tumors from patients on the multidose regimen. Day 22 biopsies were negative for viral replication.

Three of the 23 patients on the single-dose regimen had formal partial responses (PR) of the injected tumor and nine had tumor stabilization (8+–16+ wk). In addition, three patients with stable disease had ≥50% necrosis of the injected tumor. In contrast, three of nine patients on the multidose regimen had PR's and an additional three had stabilization with significant necrosis; only two patients had progressive disease. One patient received seven treatments over 7 mo while maintaining a partial remission. These results are consistent with experiments comparing these two regimens in nude mouse human tumor xenograft models (D. Kirn, publication pending). Responding patients included some with positive baseline neutralizing antibodies and tumors with a normal *p53* gene sequence. However, definitive correlations between these variables and the degree of tumor response cannot be made until larger phase II trials are completed.

2.2. Phase II trial: Head and Neck Cancer

Based on these results, two phase II trials in head and neck cancer patients were initiated. In a study using ONYX-015 treatment alone, approximately 30 patients refractory to chemotherapy or radiotherapy following recurrence are being treated with ONYX-015 alone; final data are pending. This clinical trial protocol is the subject of this chapter. In a second phase II trial, patients are treated simultaneously over 5 d with ONYX-015 intratumorally and cisplatin (day 1 bolus) and continuous infusion 5-fluorouracil (days 1–5) intravenously. These patients are all chemotherapy-naive in the setting of recurrent disease.

3. Material and Methods

3.1. ONYX-015 Viral Therapeutic Construct and Production

ONYX-015 is an E1B-55 kDa gene-deleted adenovirus that selectively replicates in and lyses *p53*-deficient tumor cells. The virus contains a deletion between nucleotides 2496 and 3323 in the E1B region encoding the 55 kDa protein. In addition, a C to T transition at position 2022 in E1B generates a stop codon at the third codon position of the protein. These alterations eliminate expression of the E1B 55 kDa gene in ONYX-015 infected cells. Viruses were grown in the human embryonic kidney cell line HEK293 and purified by CsCl gradient ultracentrifugation as previously described.

3.2. Study

3.2.1. Objectives

1. Primary End Points
   - Objective response rate of injected target tumors: Percent of patients with PRs or complete responses (CRs).
   - Pain response rate: Percent of patients with a 50% reduction in pain or pain medication usage (≥4 wk): pain assessment by visual analog pain scale.
   - Safety of intratumoral injections of ONYX-015: assessment of local, systemic toxicities
2. Secondary End Points
   - Progression-free survival
   - Survival
   - Quality of life (assessed by EORTC global QLQ-C30 and EORTC disease specific QLQ -H&N35)
   - Performance status response: Percent of patients with a ≥20 point increase in Karnofsky performance status (≥ 4 wk).
   - Immune response: neutralizing antibody response

3.2.2. Study Design

This phase II study is designed to evaluate the efficacy and safety of Onyx's attenuated adenovirus, ONYX-015, when administered intratumorally to patients with recurrent and refractory head and neck cancer. Patients eligible for study participation will have unresectable disease, which is refractory to at least one prior chemotherapeutic regimen and/or radiation therapy. The efficacy of ONYX-015 treatment will be evaluated based on the injected tumor(s) response. The clinical benefit of ONYX-015 will be evaluated through quality-of-life assessment (EORTC instrument), Karnofsky performance score, and pain assessment. Survival and progression-free survival intervals will also be recorded. The humoral (antibody-mediated) immune response will be evaluated to determine its potential for affecting efficacy or safety.

3.2.2.1. ONYX-015 Dosages and Dosing Rationale

Eligible patients will be treated with ONYX-015 administered daily for 5 d at a dose of 10^{10} pfu per day. This was the highest dose administered daily for 5 d in the phase I study and was shown to be safe (i.e., no dose-limiting toxicities).

3.2.2.2. Treatment with ONYX-015

a. Dosing Regimen: For administration of each dose of ONYX-015, patients will be treated and observed in a properly equipped outpatient clinic. The target tumor will be injected with 10^{10} PFU of ONYX-015 daily over 5 d (i.e., a total dose 5×10^{10} PFU) (with day 1 being the first day of ONYX-015 injection (*see* **Note 1**). Nontarget tumor(s) (where applicable) may be injected with either diluent or ONYX-015 on the same days in identical fashion to the target tumor following the guidelines detailed in **steps 2c** and **3** below.
b. Target Tumor Masses: The dominant, symptom-causing tumor (if symptoms are present) should be identified as the target tumor and should be the only tumor injected with ONYX-015 during the first two treatment cycles. The identification of the most symptomatic, problematic lesion is based on the judgement of the Principal Investigator. Multinodular, but contiguous tumors can be treated and evaluated as a single lesion.
c. Secondary, Nontarget Tumor Masses: If additional, smaller, accessible lesions are present, these lesions may be injected with diluent for the first two treatment cycles as described in **step 3** below. Thereafter, treatments may be divided between up to three separate lesions (i.e., the initial two cycles must be concentrated within the dominant lesion; thereafter, 6 wk after treatment initiation, two additional secondary lesions may be injected). However, the total dose to the patient will remain the same (i.e., the same total dose will be divided up between the tumors to be treated); the total volume in which the ONYX-015 is suspended will be increased based on the total tumor volume of the tumors to be treated. If a CR occurs in a treated lesion, injections can be continued as outlined above with newly defined dominant and secondary lesions.
d. Immediate Posttreatment Monitoring of Patients: The patient's vital signs will be taken ≤15 min before each ONYX-015 injection. After each injection is completed, the patient will be observed in the clinic for a minimum of 30 min. Vital signs will be taken after 30 min ± 5 min. If vital sign(s) have changed by >15%, vital signs will be repeated every 30 min until returning to within baseline 15% of baseline values. Following the observation period, the patient will be sent home or hospitalized overnight at the discretion of the investigator.

3.2.2.3. Repeat Treatment

At the discretion of the Principal Investigator, patients will be eligible for repeat treatment cycles of ONYX-015 at the same dosage every 3 wk (counting from the day 1 of the previous treatment cycle) if they meet the following criteria:

- No grade 4 toxicity with the prior treatment cycle of ONYX-015. Patients experiencing grade 4 toxicity will be eligible for repeat dosing at 10^8–10^9 PFU per day for 5 d at the discretion of the Principal Investigator after consultation with the Onyx Medical Director.
- No evidence of progressive disease at the target tumor site following at least two treatment cycles with ONYX-015.
- No interim development of any withdrawal criteria (**Subheading 3.2.3.**).

3.2.3. Study Population

3.2.3.1. Squamous Cell Carcinoma of the Head and Neck

Squamous cell carcinoma of the head and neck afflicts an estimated 125,000 patients annually in developed countries in Europe, North America, and the Far East. In the U.S., the annual incidence is estimated at 45,000 cases with 15,000 associated deaths. Head and neck tumors have been reported to harbor *p53* mutations in 45–70% of cases; both alcohol and tobacco use are associated with these mutations. Primary therapy for localized disease is surgery and adjuvant radiotherapy.

Tumors recur in approximately one-third of patients following surgery. In the majority of cases, they recur in the region of the original primary tumor and lead to severe morbidity because of pain and to oropharyngeal and laryngeal obstruction and the resultant difficulties in swallowing and speech. Once the cancer has recurred and/or metastasized, the patient is considered incurable. Palliative surgery is difficult and disfiguring, and further radiation therapy is not generally beneficial for more than a few months. Several chemotherapeutic agents have been used in recurrent squamous cell carcinoma of the head and

neck. Combination regimens have been shown to induce responses in 30–40% of patients, but the therapy can be toxic and there is no clear impact on survival. Once a patient's tumor is refractory to chemotherapy and/or radiation therapy, the median life expectancy is 3 mo and tumor response rates to second or third-line chemotherapeutic agents are 15%. There remains an urgent need for more effective therapies for these terminally ill patients.

3.2.2.2. Inclusion Criteria

For inclusion in this study, a patient must satisfy the following criteria:

Tumor status

- Histologically confirmed squamous cell carcinoma of the head and neck, including the oral cavity, pharynx, and larynx
- Recurrent disease, which is refractory to radiotherapy and/or chemotherapy. Recurrent disease refers to tumor that progresses following primary therapy (surgery and/or radiation and/or chemotherapy) and therefore may include locally advanced tumors which progress following primary treatment with surgery and/or radiation and/or chemotherapy.
- The entire tumor is amenable to direct injection in the clinic as described in the protocol
- Tumor amenable to measurement clinically and/or radiographically
- Tumor is unresectable (as defined by attending surgeon)

General

- Karnofsky Performance Status of ≥70% (**Subheading 3.2.6.**).
- Life expectancy of ≥3 mo.
- ≥18 yr of age (or the age of majority if different than 18 yr of age)
- Consent for study participation given before screening and treatment, as evidenced by patient's dated signature (or signature of legally acceptable representative, if patient unable to give informed consent).

3.2.3.3. Exclusion Criteria

Patients with any of the following will be excluded from the study:

- Ongoing active infection, including human immunodeficiency virus
- Viral syndrome diagnosed within the last 2 wk.
- Chemotherapy within the last 3 wk.
- Radiotherapy to the target tumor site within the last 4 wk.
- Concomitant hematological malignancy (e.g., chronic lymphocytic leukemia, non-Hodgkin's lymphoma).
- Impending airway obstruction or other condition requiring urgent (predicted within 2 wk) tumor debulking.
- Pregnant or lactating females.
- Prior participation in any research protocol, which involved administration of adenovirus vectors.

- Treatment with any other investigational therapy within the last 6 wk.
- Any condition that compromises compliance with the objectives and procedures of this protocol, as judged by the investigator.

3.2.3.4. Withdrawal of Patients from Study

Patients may be withdrawn from the study, in terms of no further treatment with ONYX-015, for any of the reasons listed below. The day on which this occurs will be referenced as the "day withdrawn from study treatment." The last day on which the patient is seen will be considered the "day off study." In some case(s) these dates may be the same.

- Patient's decision to discontinue study participation.
- Intolerable adverse reaction(s) (judged to be either physically or psychologically detrimental to the patient).
- Intercurrent illness that may compromise the patient's safety or interfere with the evaluation of study treatment (e.g., chronic lymphocytic leukemia, non-Hodgkin's lymphoma).
- Impending airway obstruction or other condition requiring urgent tumor debulking.
- Requirement for urgent a) radiotherapy or b) chemotherapy (for the **target** tumor site).

  Note: For any ONYX-015 treated tumor showing stable disease or objective response, such tumor may continue to be treated with ONYX-015 even if the target tumor requires radiotherapy—at the Investigators discretion.
- Requirement for concomitant medication that may interfere with the evaluation of study treatment, including chronic immunosuppressive medication, e.g., glucocorticoid or cyclosporine, unless investigator and Onyx Medical Director or project manager mutually determine that patient's status warrants continuation on study treatment (*see* **Note 2**).

Pregnancy

- Clinical evidence of progressive disease at the *target* tumor site after a *minimum of 2 cycles of treatment.*
- Failure to comply with study procedures.
- Loss of patient to follow-up.

3.2.3.5. Sample Size

Staged accrual will be used such that the study will be terminated after specific numbers of patients have been enrolled if a minimum number of responses have not been seen; the lowest significant response rate to be ruled out will be 20% (at alpha = 0.10; beta 0.10). If at least the minimum number of objective responses are seen to allow completion of accrual, a total of 30 evaluable patients will be accrued. For example, if no responses (symptomatic or shrinkage) are seen in any of the first 12 patients treated, or only 1 out of the first

20, the study would be terminated at that time. The estimated confidence interval on the response rate is ≤ (±)20 %.

Evaluable Patients: An evaluable patient is any patient who meets the enrollment criteria, receives at least two cycles of treatment, and has follow-up through the end of the second cycle with radiographic imaging (following the radiographic imaging guidelines) and/or adequate measurement by physical exam before and after treatment.

Correlations: An additional 10–20 evaluable patients may be enrolled (optional) in order to gain statistical power to allow meaningful comparisons between different subgroups of patients, should these appear critical to the planning of a pivotal trial with ONYX-015. These analyses might compare patients with 1) large vs small tumors (> or <10 cm^2), 2) differing *p53* status as defined by immunohistochemistry or sequenceing for *p53* (+/– normal), 3) the presence or absence of pre-treatment neutralizing antibodies (+/–).

3.2.4. Conduct of the Study—Schedule of Activities and Evaluations

3.2.4.1. Screening and Pretreatment

A checklist of screening and pretreatment evaluations follows.

- Signed IRB- or LREC-approved informed consent
- Testing of tumor biopsy by immunohistochemistry (IHC) and *p53* gene sequencing for *p53* status (results not required prior to patient's treatment with ONYX-015). Biopsy material must have been obtained from the *target* tumor after becoming refractory to chemotherapy and/or radiation therapy.
- Complete medical history
- Complete physical examination, including vital signs, weight, and height
- Karnofsky performance score
- Hematological tests, including prothrombin time (PT) and INR, and partial thromboplastin time (PTT)
- CD3, CD4, CD8, and total lymphocyte counts
- Serum chemistry tests
- Serum antibody to type 5 adenovirus (neutralizing)
- Plasma sample for PCR testing for the presence of adenovirus, ONYX-015 DNA
- Archival plasma sample
- Urinalysis
- Urine or serum pregnancy test, if applicable
- Electrocardiogram (12-lead)
- Chest X-ray (PA and lateral)
- Delayed-type hypersensitivity skin testing
- Secondary diagnoses
- Baseline medical events, including signs, symptoms, and illnesses
- Medications within the last 2 mo
- EORTC quality-of-life assessment

- Pain evaluation: visual analog pain scale, pain medication usage
- Tumor size assessment by CT or MRI scan (excluding tumors evaluable by physical exam, but *not* by radiography):
  — cross-sectional area (computer-assisted measurement)
  — cross-sectional area (classical measurement)
  — non-necrotic volume (computer-assisted measurement)
- Clinical assessment of the tumor (size, consistency, color)
- Photography of tumor (if externally visible)

3.2.4.2. Enrollment

Upon completion of the above screening procedures, each eligible patient will be enrolled. Each patient will be assigned a unique patient identification number. The patient number will be sequentially assigned to correspond with the order of enrollment into the study. This number along with the patient's initials will be documented on each page of the CRF. For patients who are screened for study participation, but who are not enrolled, CRFs recording the screening data collected, including reason not enrolled, will be completed.

3.2.4.3. Out-Patient Follow-Up During ONYX-015 Treatment Period

The same schedule and visit requirements (except where differences are specified below) will be followed for each treatment cycle, including the initial ONYX-015 treatment cycle and any repeat treatment cycles (where later applicable). Any deviation from stated schedules must be approved by Onyx's Medical Director or either of the project managers.

3.2.4.4. Post-Treatment Monitoring of Patients

The patient's vital signs will be taken ≤15 min before each ONYX-015 injection. After each injection is completed, the patient will be observed in the clinic for a minimum of 30 min. Vital signs will be taken after 30 min ± 5 min. If vital sign(s) have changed by >15%, vital signs will be repeated every 30 min ± 5 min until returning to within 15% of baseline values < +/– 15%. Following the observation period, the patient will be sent home or hospitalized overnight at the discretion of the investigator.

Day 5 (± 2) Prior to the tumor injection on that day blood will be drawn for

- Hematological tests, including prothrombin time (PT), INR and partial thromboplastin time (PTT)
- Tumor bandage evaluation/changing, as required; assessment of drainage
- Photography of target tumor (optional)
- Serum chemistry tests
- Adenovirus DNA in blood by PCR

Day 15 (± 2)

- Aspiration and measurement of necrotic tumor tissue/fluid (if present)

- Brief physical examination directed to relevant signs and symptoms, including vital signs and weight.
- Tumor bandage evaluation/changing, as required; assessment of drainage
- Photography of target tumor (optional)
- Hematological tests, including PT, INR, and PTT
- Serum chemistry tests
- Adenovirus DNA in blood by PCR (test to be performed if PCR positive on day 5 specimen)
- Changes in concomitant medications
- Reporting of adverse events
- Patients to be given visual pain scales, to be completed daily (one per day upon returning) until Day 22 visit

Days 22 (± 2)

- Clinical assessment of the treated tumors (size, consistency, color, etc.)
- Tumor size assessment by CT scan, MRI, or physical exam
- Complete physical examination, including vital signs and weight
- Karnofsky performance score
- Tumor bandage evaluation/changing, as required; assessment of drainage
- Photography of target tumor
- Hematological tests, including PT, INR, and PTT
- Serum chemistry tests
- Serum antibody to Ad5/ONYX-015 (neutralizing)
- Adenovirus DNA in blood by PCR (test to be performed if PCR positive on day 15 specimen)
- Archival plasma sample
- Urinalysis
- Pain evaluation: pain medication usage, visual analogue pain scales to be collected from patients
- EORTC quality of life assessment
- Changes in concomitant medications

3.2.4.5. Long-Term Follow-Up After Completion of ONYX-015 Treatment

Once patients have completed treatment with ONYX-015, they will be followed until target tumor progression as follows: every 4 wk for 6 mo, and every 3 mo thereafter for 6 mo (for a total of 12 mo from the end of the last ONYX-015 treatment cycle). (For the purposes of this study, 1 mo equals 4 wk, or 28 d). The date of death, if applicable, will be determined for all patients. The checklist below details procedures to be performed at each of these follow-up visits. The visits occurring every 4 wk may occur ± 1 wk, and all quarterly visits (after 6 mo) may occur ± 2 wk. The investigator may order other procedures as needed, based on the patient's clinical status. It is to be noted that the quarterly follow-up visits after the 3-mo visit may be performed at the study center or, if a patient is unable to return to the study center, the

patient's primary oncologist may perform the assessments and provide the data to the study center using worksheets specially developed for this purpose.

- Brief physical examination directed to relevant signs and symptoms, including vital signs and weight
- Karnofsky performance score
- Tumor size assessment by CT scan, MRI, or physical exam
- Clinical assessment of the tumor (size, color, consistency, etc.)
- Tumor bandage evaluation/changing (if required), assessment of drainage
- Photography of target tumor
- EORTC quality of life assessments
- Pain evaluation: visual analog pain scale, pain medication usage
- Changes in concomitant medications (*see* **Note 3**)
- Reporting of adverse events (*see* **Note 4**)

3.2.5. Tumor and Patient Assessments

3.2.5.1. Tumor Response Criteria

Using the following standard criteria, response is to be assessed separately on the injected target tumor, injected nontarget tumor(s) (including those injected with diluent) and noninjected tumor foci according to the schedule outlined above in **Subheading 3.2.4.** for "tumor size assessment." Duration of response and progression-free survival will be determined. *Classical/standard* cross-sectional tumor measurements used to assess response should be the following: (maximal tumor diameter × perpendicular diameter).

Complete response (CR): complete disappearance of tumor
Partial response (PR): regression of the tumor(s) by ≥50% but <100%
Minor response (MR): regression of the tumor(s) by ≤25% but <50%
Stable disease (SD) tumor decrease or increase in size by <25%
Progressive disease (PD): ≥25% increase in tumor size

3.2.5.2. Clinical Benefit Response Criteria (Pain, Performance Status)

- Pain response: A ≥50% reduction in pain and/or pain medication usage lasting ≤ 4 wk. Patients must have a baseline visual analogue pain score ≥20 in order to be evaluable for pain response.
- Performance status response: A ≥20-point increase in KPS lasting ≥4 wk. Patients must have a baseline ≥ KPS of 70 to be evaluable for performance status response.
- Weight changes of patients will be recorded during time on study.

3.2.6. Statistical Methods and Data Analysis

The primary objectives of this study are to estimate the objective response rate (tumor size and pain) and toxicity associated with ONYX-015 when administered into solid squamous cell carcinoma of the head and neck.

Secondary objectives are: 1) to estimate response rates using classical maximal cross-sectional measurements; 2) to estimate survival and time to disease progression; 3) to assess the quality of life benefit of ONYX-015; 4) to evaluate the performance status response, and 5) to determine the local and systemic immune response to ONYX-015.

3.2.6.1. Sample Size Considerations

A staged accrual design will be used for this study. In the first stage, 12 patients will be enrolled and treated with ONYX-015. If none of the patients respond to treatment, then enrollment into the study will be terminated. If at least one patient responds to treatment, then enrollment may be continued. If, after the enrollment of 20 patients at least two patients respond to treatment, then enrollment will be continued until a total of 30 "evaluable" patients have completed two cycles of treatment (*see* **Subheading 3.2.3**).

Assuming the study goes to completion of all 30 evaluable patients in planned enrollment, then the 90% confidence interval for the estimated response rate will be (±) 12%, assuming 20% responders. Sufficient evidence to indicate that the true response rate is greater than 20% would be provided if the lower limit of the confidence interval is greater than 0.20 ($\alpha = 0.05$, 1-tailed test).

3.2.6.2. Primary Efficacy Analysis

Because this is an uncontrolled study enrolling a small number of patients, formal hypothesis testing is not planned. However, comparisons of different subgroups may lead to the generation of hypotheses which will be studied prospectively in subsequent clinical trials.

The primary statistical analysis will be the estimation of the 95% confidence interval of the probability of response, defined as partial or complete response in injected target tumors using computer-assisted cross-sectional measurements (*see* **Subheading 3.2.5.**). The confidence interval will be determined using the binomial distribution. The proportion of patients with partial or complete response using computer-assisted non-necrotic volume measurements and the proportion of patients with a ≥50% reduction in pain as determined using Visual Analog Scales or pain medication usage will be estimated similarly.

The definition of response requires two observations a least 4 wk apart. The primary analysis, therefore, will be done on the following two groups of patients:

Evaluable: Patients who meet the enrollment criteria and receive at least two cycles of treatment, and have follow-up data through the end of the second cycle with radiographic imaging and/or adequate measurement by physical exam before and after treatment.

Intent to Treat: Patients who received at least one administration of study medication.

3.2.6.3. Secondary Efficacy Analysis

Secondary analyses will include the following:

- The proportion of patients with stable disease at the target tumor site using computer-assisted cross-sectional measurements (defined in **Subheading 3.2.5.**)
- The proportion of patients with partial or complete responses (defined in **Subheading 3.2.5.**) using classical maximal cross-sectional measurements
- Time to disease progression estimated by the method of Kaplan and Meier
- Survival evaluated with Kaplan Meier estimation
- Quality of life as assessed by EORTC global QLQ-C30 and EORTC disease specific QLQ-H&N35
- The proportion of patients with a ≥20-point increase in Karnofsky performance status (≥4 wk)

Relationships with the following variables will be examined as appropriate (these comparisons might generate hypotheses which could be addressed subsequently in prospectively designed trials):

- Baseline immunological status: CD3, CD4, and CD8 counts plus delayed-type hypersensitivity skin response
- Neutralizing antibody titer at baseline and end of treatment cycle
- Baseline tumor size (> or <10 cm^2)
- *p53* gene sequence, *p53* immunohistochemical test results

3.2.6.4. Demographics and Baseline Characteristics

Subject age, weight, and height will be summarized with descriptive statistics (mean standard deviation, minimum and maximum), whereas gender and race will be summarized with frequency tabulations. Individual patient listings will be produced. Medical history data will be summarized with frequency tabulations.

3.2.6.5. Safety Data

Patients who receive at least one treatment with study medication (*evaluable for safety)* will be included in the safety analysis. Safety data including adverse events, laboratory results, toxicity, vital signs, and withdrawal information will be summarized over time. Individual patient listings will be produced. Data will also be listed by patient for physical examinations, electrocardiograms, and chest X-rays.

Adverse events will be coded with the COSTART coding thesaurus and tabulated using the COSTART body system classification scheme. The number and percent of subjects with adverse events will be tabulated; in addition,

the data will be stratified by adverse event intensity and investigator-specified relationship to ONYX-015.

3.2.6.6. Concomitant Medications

All concomitant medication usage documented during the study period will be summarized in frequency tabulations. The Anatomical Therapeutical Chemical (ATC) coding scheme will be used to group medications into relevant categories for these tabulations.

4. Notes

1. Intratumoral injection technique: the most common problem encountered with the intratumoral injection treatments described in the protocol is suboptimal intratumoral distribution of the virus. The injection needle should be passed to its greatest depth initially, and the virus-containing solution should be injected as the needle is being withdrawn. This technique ensures distribution of the virus along the entire needle tract. In addition, injection should be out to and 0.2–0.5 cm. beyond the palpable edge of the tumor. This is to ensure that microscopic tumor deposits beyond the palpable tumor edge can be targeted with the viral therapy.
2. Limited courses of glucocorticoid therapy are allowable (e.g., for nausea control).
3. After the 1-mo follow-up visit, the only concomitant medications that will be recorded are those, if any, that are relevant to an adverse event (ongoing or delayed in onset) judged to be potentially causally related to ONYX-015 and antitumor therapy(ies).
4. After the 1-mo follow-up visit, only those adverse events (ongoing or delayed in onset) judged to be potentially causally related to ONYX-015 will be recorded.

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II

Clinical Protocols for Cancer Gene Therapy

D: Antisense Gene Therapy